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RHEUMATIC PERICARDITIS IN CHILDHOOD

BY

LEONARD FINDLAY, M.D., D.Sc., JAMES W. MACFARLANE, M.B., Ch.B.,

and MARY M. STEVENSON, M.A., M.D.

(From the Department of Pædiatrics, Glasgow University, and the Royal Hospital for Sick Children, Glasgow.)

Our work on rheumatism has necessitated a careful scrutiny of the case histories of all examples of the disease which have come under our observation. During the course of this survey there have emerged several facts in its life history which seem worthy of record, since they appear to be somewhat at variance with current teaching. Of these perhaps the most striking is the almost invariable association of pericarditis with arthritis, and, in contrast to what is generally believed, the slight degree of correlation between it and chorea.

Since much of the argument in the present communication is based on clinical experience a crucial question is the ability to diagnose the condition of pericarditis during life and to say with any degree of certainty whether it is or is not present. All clinicians will agree that in its milder forms it is most elusive. This is especially true during infancy when pericarditis, commonly, however, of a purulent nature, is usually only discovered at autopsy. Some writers, however, have stated that when rheumatism attacks the heart the whole organ (endocardium, myocardium and pericardium) is involved. As Sturges[1] has said, 'the rheumatic heart inflammation of children when pericardial is always endocardial as well, and when endocardial is extremely likely, with the recurrence of rheumatism, to involve the pericardium also.' This may be true if the statement is confined to the recurrence of rheumatism, but it is surprising to us to learn that Sturges noted that 'out of 100 fatal cases of heart disease occurring at the Children's Hospital, Great Ormond street, between June, 1881, and April, 1892, of which 54 were of rheumatic origin and 46 due to other causes, in 6 only was there no evidence of pericarditis.' Roberts, who quoted the above, remarks that his experience is in complete accord with that of Sturges, and Cheadle[2] states that 'pericarditis is almost always found post mortem in the fatal heart disease of children.' Should such a state of matters really be the case then it would appear futile to discuss the question of pericarditis apart from carditis and to attempt to express in figures the relative frequency with which pericarditis is associated with one or other manifestation of rheumatism. That it is true, however, we very much doubt, even although it bears the impress of authorities like Sturges and Cheadle.

At the Royal Hospital for Sick Children, Glasgow, we have records of 30 post-mortem examinations in children dying from all forms of rheumatic heart disease, and only in 15, i.e., 50 per cent., was there implication of the pericardium. If the cases in which pericarditis was discovered before death are excluded, we are left with 19 cases, and in only 4 of these was involvement of the pericardium an accidental finding. In one of these four cases the pericardium was densely adherent from mischief occurring apparently two years previously, and in the other three the inflammation of the pericardium was very early and of moderate degree. Thus our experience is at variance with that of Roberts, Sturges and Cheadle and in our opinion justifies from clinical evidence the consideration of the relationship of pericarditis to other rheumatic phenomena.

We have records of 51 examples of rheumatic pericarditis admitted to the Royal Hospital for Sick Children, Glasgow, between 1915 and 1928 inclusive. The sequence of events in all the cases reviewed is given in Table 1, and summaries of the clinical histories of those patients in whom chorea occurred are given in the appendix.

A. Cases in which the heart alone was involved. In 4 of the cases (No. 2, 36, 45 and 51) the cardiac condition was the only manifestation of the mischief but that this was of a rheumatic nature we have no doubt. In one (No. 2) there occurred at the age of 7 years and 10 months a typical attack of pericarditis from which the boy recovered, though he has been left with some enlargement of the heart, a loud and definite musical mitral systolic murmur and dyspnœa on exertion. Another of the patients (No. 45) was a girl who had had a cardiac murmur since an attack of scarlet fever at 2 years : she came under our observation at the age of 5 years with typical pericardial effusion during the course of which a crop of subcutaneous nodules appeared on the elbows, knuckles, knees and ankles. This girl died from a failing heart at the age of 7 years, when an adherent pericardium and botton-hole mitral orifice were discovered at the autopsy. Another of these patients (No. 36) was a girl who came under observation at the age of 9 years with a history that at the age of 7 years she had been attacked with vomiting, cardialgia and orthopnœa, when the doctor diagnosed a ' very bad heart.' There had never been any complaint of pain in the joints or of tonsillitis, and none of the relatives had ever suffered from rheumatism. After this illness, which lasted for three months, the girl had remained fairly well till one week previously, when she developed a headache, was sick and vomited, and had a return of the præcordial pain and dyspnœa. On admission there was slight fever, the heart was very much enlarged, and a loud systolic murmur was audible at the mitral area and well conducted to the axilla. The child's condition rapidly deteriorated and she died two weeks after admission to hospital. At the autopsy were found a densely and diffusely adherent pericardium, and enlargement of the heart; and fresh minute vegetations were discovered on both the aortic and the mitral valves. The fourth purely cardiac example (No. 51) of rheumatism in this series was a boy of $5\frac{1}{2}$ years. This child had been taken ill three weeks before coming under observation with severe pain over the heart and the right side of

abdomen, and was admitted to a surgical ward as a case of appendicitis. No operation was performed and all pain having disappeared after a week's residence the child was dismissed; but the first night he was home the pain returned, and continuing to be severe, he was readmitted, but to a medical ward. There was only slight fever (101° F.), the pulse numbered 130, the heart was much enlarged, and all over the præcordia, but loudest at the apex and well conducted to the left, a loud systolic murmur was audible. The child died after 20 days, and during the last week of his illness fever, which had disappeared on the day after admission, returned. At autopsy the pericardial sac was found to contain an excessive amount of a slightly turbid fluid, and both visceral and parietal layers of the pericardium were injected. The heart was enlarged and fresh typical rheumatic vegetations were found on the cusps of the mitral valve. In this case also no history of any other rheumatic manifestation, either in the child himself or in his relatives, could be obtained.

B. Cases with pericarditis as the sole cardiac lesion. In 2 of the cases (No. 22 and 30) pericarditis apparently was the sole cardiac lesion. At least no cardiac murmur suggesting endocardial disease, either at the time of the acute cardiac illness or subsequently, could be made out. As both of these patients recovered this limitation of the rheumatic mischief to the pericardium must remain problematical. Both children had suffered from arthritis, and in neither was there a history of chorea.

C. Cases with arthritis and pericarditis.—44 of the 51 patients had suffered at some time or other from arthritis. In 17 the arthritis preceded by a definite period the appearance of pericarditis. In 26 patients the pericarditis ensued during the attack of arthritis, on 14 occasions during the first attack, on 10 during a second attack and on 2 occasions during a third attack. In 1 of the cases (No. 37) the pericarditis occurred prior to the other manifestations (chorea, arthritis and endocarditis,) of rheumatism.

D. Cases with chorea and pericarditis.—15 of the patients had suffered from chorea, but 13 of them had also had arthritis, so that in only 2 children was chorea the sole other rheumatic manifestation than the cardiac involvement. One of these children (No. 47) had suffered from chorea with endocarditis 2 years prior to the attack of pericarditis; while in the case of the other (No. 27), in which the history left something to be desired, pericarditis and endocarditis immediately preceded the onset of chorea. Both of these children died from the illness of which the pericarditis was a manifestation, so that it is possible that if they had survived, arthritis might have ensued at a later date. In 6 of the choreic cases, including the one mentioned above, the attack of chorea had occurred a considerable time before the development of pericarditis; in 2 of the cases the attack of chorea occurred after the onset of pericarditis; in 5 the pericarditis developed while the chorea was present, but in three of them there was also arthritis at the same time. Thus in only 2 of the cases did chorea and pericarditis occur simultaneously when there could be any question of considering one a complication of the other.

Chorea and arthritis occurring simultaneously.—At this point it is appropriate to make some mention of the simultaneous occurrence of arthritis and

TABLE I

SHOWING SEQUENCE OF EVENTS IN CASES OF PERICARDITIS.

(In this table A signifies arthritis; G.P. growing pains; C chorea; E endocarditis; P pericarditis and N nodules. When the manifestations occurred synchronously the symbols are united by a + sign.)

Case No.	Sex	Age at onset of pericarditis in years	Rheumatic Attacks							Result
			1st	2nd	3rd	4th	5th	6th	7th	
1	M.	11	G.P.	A+E+P						
2	M.	$7\frac{10}{12}$	P+E							
3	M.	13	A+E	P						
4	M.	$6\frac{1}{4}$	A+P+E							
5	M.	$10\frac{1}{3}$	A+E+P							Died
6	M.	11	A+E	P						Died
7	M.	10	A	A	A+E+P+N*					
8	M.	5	A	E	P					Died
9	M.	$8\frac{1}{2}$	A	A	A+E+P	A*				
10	M.	9	A	E+P						
11	M.	5	A	A+E+P						
12	M.	$11\frac{1}{2}$	A+P+E+N	A						Died†
13	M.	7	A+E	P						Died
14	F.	6	C+E	A	P					
15	F.	9	A+P+E							
16	F.	$7\frac{1}{4}$	A+E	P						Died
17	F.	$7\frac{1}{2}$	A+E+P+N							Died
18	F.	12	C	A+P+E						Died
19	F.	8	A+P+E							Died
20	F.	$11\frac{1}{2}$	A	C+E	A+P					Died
21	F.	7	A+E	C	P					
22	F.	9	A+P							
23	F.	$6\frac{1}{2}$	A+E+C+P							
24	M	$7\frac{2}{3}$	A+E+P							Died
25	F.	12	G.P.	C+E+P	C+P					Died
26	F.	10	C+A+E+P							Died
27	F.	5	P+E+C							Died
28	F.	9	A+E	P						Died
29	F.	9	A+P+E	A						
30	F.	11	A	A+P						
31	F.	$13\frac{1}{2}$	A+P+E							
32	F.	11	A+E+P							
33	F.	7	A	A+E+P						
34	F.	$10\frac{1}{2}$	A	P+E						Died
35	M.	6	A+E	A+P						Died
36	F.	7	P	E						Died
37	M.	5	P	C+A+E						Died
38	F.	$8\frac{11}{12}$	A	E+P						
39	F.	$11\frac{3}{4}$	A+E	P						
40	F.	9	A	A+P+E						
41	F.	$10\frac{1}{2}$	A	C+E+P						Died
42	F.	11	A+C+E	A+P						Died
43	F.	8	C	A	C+E	C	P			Died
44	F.	7	A+E	A+P						
45	F.	5	E	P+N						Died
46	M.	$6\frac{1}{2}$	C	C+E	C	C+A+P+N				
47	F.	$11\frac{9}{12}$	C+E	P						Died
48	F.	10	A+E+N	A+N	P+N					
49	F.	11	C	C+?E	A	C+E	C	A	P	
50	M.	5	A	A+E+P						Died
51	M.	$5\frac{1}{2}$	E+P							Died

*The fact that in these cases the endocarditis is associated with thethird rheumatic attack would seem opposed to what we have already written, viz. :—that heart in our experience is usually affected during first two rheumatic attacks. We only obtained a history of the first two attacks in these cases and did not observe the children till during the third attack when the heart was already found affected.

†1 year later of decompensation.

chorea. Though a history of chorea and arthritis occurring simultaneously is often obtained from the parents, it is in our experience one of the rarest phenomena. In fact, in only 5 of the 51 children who suffered from pericarditis did chorea and arthritis occur anything like synchronously. This does not of course mean that we have not more frequently observed these two manifestations follow closely on one another. An acute painful arthritis has never been observed along with an active chorea while the cases have been under observation in hospital, unless in hemichorea when the muscular contractions and the arthritis were on opposite sides of the body. We have seen the one follow immediately on the heels of the other, with perhaps the swelling of the joints persisting after the appearance of chorea, but by which time all pain and tenderness had disappeared. We have also observed alternation of the two—chorea subsiding, to be replaced by arthritis, and after its disappearance chorea returning. One can imagine the excruciating suffering which the child would endure did chorea and arthritis occur together. We have seen sedatives administered for the control of the movements, but never because they seemed to be causing the child any special pain.

The alternation of chorea and arthritis has been noted by most authors and even the early writers, e.g., Copland[3], Bright[4], Begbie[5] and Churchill[6] call attention to it; but never does one find a mention of them occurring together. In fact Roger[9], and still later Radcliff[25], said they were antagonistic, a dictum which was reiterated a few years ago by Pfaundler[7]. Lepehne[8], who took Pfaundler to task for making such a statement was, however, only able to unearth two recorded examples of this phenomenon after a thorough search of the literature. Both cases emanated from Senator's clinic and in one of them Lepehne states that the chorea caused such acute pain that morphia had to be administered for its relief. These two cases on account of their extreme rarity rather throw into relief, than detract from, the general truth of Roger's axiom. We know the tendency in rheumatic arthritis for the mischief truly to flit from joint to joint, and Goodhart and Still[10] have remarked that when endocarditis or pericarditis develops it is usual for chorea if present to disappear, so that by analogy alone one would not expect chorea and arthritis to occur simultaneously.

Sex incidence of pericarditis.—Of our cases of pericarditis 32 were females and 19 males, which is a proportion somewhat different from that usually recorded. Still[11] for instance states that of 53 examples of pericarditis observed by him 32 were boys and 20 girls; and he contrasts, as most authors do, the sex incidence of this manifestation with that of chorea. We find, however, that Sibson[12] notes that of his cases of rheumatic pericarditis under 20 years of age males and females were equally affected (17 of each) whereas of the 29 patients over 20 years of age 18 were males and 11 females. Church[13] also states that he did not find in his experience the reputed great preponderance of males, and Cheadle[2] in his classical article in Allbutt's System of Medicine does not touch at all on the sex incidence of pericarditis. Most authors, however, agree with Still, and the different sex incidence of pericarditis and chorea

was indeed used as an argument in the early days to contravert the theory that pericarditis was the cause of chorea.

In our experience the sex incidence of chorea and pericarditis is the same, though, as we have shown above, it is comparatively rare to have the two diseases in the one individual. So far as the sex incidence of chorea is concerned our experience coincides with that of other authors (Table 2).

TABLE 2

SEX INCIDENCE OF CHOREA

	Males	Females	Total.
R.H.S.C., Glasgow	27·5%	72·4%	276
Still[14], London.	28·0%	72·0%	150
Bendix[15], Berlin.	26·0%	74·0%	—
Kerley[16], New York.	40·0%	60·0%	—

Age incidence of pericarditis.—The earliest age at which we diagnosed the condition was five years but, as in one of these cases (No. 37) the pericardial sac was found at post-mortem examination obliterated by dense fibrous adhesions, the mischief must have commenced at a much earlier date. It was impossible from the history to hazard an opinion regarding the date of onset of the pericarditis. As seen from the age distribution of the cases coming under our observation given in Table 3, it would seem to be relatively more frequent in the earlier years of childhood.

TABLE 3

AGE DISTRIBUTION OF CASES OF PERICARDITIS.

Age in years ..	5	6	7	8	9	10	11	12	13
No. of cases	7	5	9	4	6	6	10	2	2
	21			16			14		

It is unsafe, however, to draw any definite conclusion from this material as in a children's hospital the younger children form a much greater proportion of the patients. The experience of Sibson[12] lends some support to our figures since he writes that though he observed more cases of rheumatism after 20 years of age than before 20 years of age, a larger proportion of the latter developed pericarditis, in fact 25 per cent. of the latter as against 16 per cent. of the former.

Association of nodules and pericarditis.—In 6 of the examples of pericarditis (Nos. 7, 12, 17, 45, 46 and 48) subcutaneous rheumatic nodules were present,

but in all there was clinical or pathological evidence of endocarditis as well. In one of the cases (No. 48) nodules appeared with each bout of the disease.

Fate of patients with pericarditis.—Of the 51 cases 26 died, 24 during the acute phase of the disease and 2 at a later date from cardiac decompensation. The gravity of pericarditis during childhood is remarked upon by Still[11] who holds that both the immediate and the remote prognosis are serious. He states that he has hardly ever seen a case, even if it recovered from the acute illness, who did not present symptoms of cardiac disability. Gairdner[28], on the other hand, says that he has never seen a patient die from rheumatic pericarditis, but then he is referring chiefly to adults and not to children.

The present condition so far as is known of the 25 cases in our series who have survived is as follows, and fully corroborates Still's contention. In 1 case there are neither signs or symptoms of cardiac disease (the child was last seen in the spring of 1928); in 7 cases there are signs of cardiac disease but no symptoms; in 9 there are definite symptoms of cardiac disability as well as signs, and in 3 the disability is extreme. 5 of the children could not be traced.

Historical survey of association of pericarditis and chorea.

All present-day authors admit that pericarditis in rheumatism is most often associated with arthritis, but they also hold that not infrequently it is dependent on chorea. Cowan's[17] statement that 'chorea is responsible for many cases of pericarditis' may be taken as typical of present-day opinion as expressed in our text-books. It is, however, difficult to understand on what grounds such a conclusion has been arrived at, since almost without exception the illustrative examples of pericarditis in the text of the various memoirs (Watson[18], Babington[19], Bright[4], Henoch[2], Ashby and Wright[21]) on the subject have, just as in our own series of cases, been associated with arthritis and not with chorea. This modern view, at least in its implication, is in marked contrast to that held by the earlier writers who believed that pericarditis was the cause of chorea.

The history of the association of chorea and pericarditis is an interesting one and reveals in a striking fashion the human failing to associate as necessarily cause and effect any two conditions which may occur simultaneously. Copland[22] receives the credit of having for the first time observed pericarditis and chorea in the one individual. In 1821 he recorded the case of a boy of 9 years who developed arthritis followed by chorea, and made a good recovery from both. Six months later cardialgia, generalized pains and anasarca appeared, and he again got well. Ten months still later chorea and arthritis returned: on this occasion the chorea was very severe and ultimately led to a generalized flaccid paresis and death. The boy, however, retained consciousness till the end and there was no nuchal rigidity: in fact, special mention is made of the flaccidity of the muscles of the neck, both of which are points of importance in view of the post-mortem findings. At the autopsy meningitis, pericarditis and ascites were discovered. As above mentioned

this is considered by most writers on the subject the first recorded example of the association of chorea and pericarditis, but in view of the meningitis discovered post-mortem, we at the present day cannot agree that the fatal illness at least was rheumatic in nature. The association of septicæmia with arthritis, pericarditis and nervous phenomena, and its confusion with rheumatism was a frequent error in pre-bacteriology days, and even yet is one which in the absence of a complete bacteriological examination of the joint effusion and cerebro-spinal fluid, or a post-mortem examination, is apt to arise. Curiously, Latham, who wrote his monumental work on Diseases of the Heart in 1820, i.e., one year before the publication of Copland's article, makes no mention during his very exhaustive consideration of pericarditis of any association of it with chorea.

In those early days the cause of chorea was somewhat of an enigma, but with the growth of rational medicine it became less and less the custom to incriminate a lesion which was not visible. In virtue of the presence of choreiform movements in gross cerebral lesions (both cerebral and meningeal) the current belief at that time was that inflammation of the coverings of the spinal cord was the causal factor. In 1839, however, Richard Bright[4] read a paper to the Medico-Chirurgical Society of London on spasmodic disease accompanying disease of the pericardium. Bright did not doubt that inflammation of the membranes of the spine could cause a chorea, but he did not think this essential as he no doubt had observed cases going to post-mortem examination in which it was absent. In this communication he recalled the above-mentioned case of Copland and recorded several observations of his own. In not all, however, can one be sure from the facts supplied that pericarditis existed, but in two there appears little room for doubt. Though the pericarditis did develop during the course of the chorea, it is interesting in view of our findings to note that in both instances there had been antecedent typical rheumatic arthritis. One of the cases was a boy of 17 years who had had arthritis which was soon followed by chorea, and in whom Bright suspected pericarditis which was verified at the autopsy. The other patient was a young woman who also had had arthritis followed by chorea, during the course of which pericardial friction appeared: this patient made a complete recovery.

As there was no evidence of any gross nervous lesion in the case submitted to post-mortem examination, Bright held that disease of the nervous system itself was not necessary, and suggested that irritation of the pericardium might be the ætiological factor, this being transmitted to the brain by the phrenic nerves 'whose terminations would be embedded in the seat of the inflammation.' He summed up his argument in these words:—

> I doubt not that in some cases the coverings of the cerebro-spinal mass may be, and are, implicated, yet I believe that the much more frequent cause of chorea, in conjunction with rheumatism, is the inflammation of the pericardium and that the irritation is communicated thence, probably, to the spine, just as the irritation of other parts, as of the bowels, the gums, or the uterus is communicated and produces the same diseases: for I do not at all incline to the belief, that inflammation, in or about the spine, is necessary to induce chorea.

Bright's theory of the cause of chorea was supported by Babington[19] who in an article shortly afterwards (1841) recorded a series of examples of

chorea which had come under his observation. He corroborated Bright's statement that chorea was not always dependent on disease of the spinal cord, and thought that the irritation might be transmitted from a distance, as in the case of disease of the heart and pericardium 'through the irritation of the plexus and ganglia which so entirely surround that organ' just as 'irregular menstruation may produce a like effect through the lumbar plexus.' In a foot-note to this article Babington mentioned that Addison had told him that he had seen a very large number of cases of chorea and only two had been without a decided mitral or left ventricular bruit: 'in these two, however, there was disease of the heart and in one case, examined after death, there was found old thickening of mitral valve and very recent pericarditis.' Babington continued 'Should further investigation prove chorea to be more immediately dependent on disease of the heart than has hitherto been suspected the merit of the discovery will certainly be due to Dr. Addison.' Of the 25 cases which Babington recorded not all would nowadays be considered examples of Sydenham's chorea. Nine, however, are typical of the condition. In three there occurred pericarditis, and in the only one in which there is no mention of arthritis he stated that the history of the illness was unsatisfactory. Arthritis occurred prior to the pericarditis in both of the other two cases; in one of them the chorea developed subsequent to the appearance of the pericarditis, and in the other the chorea and pericarditis occurred synchronously.

It was left to Begbie (1847), however, to put the relationship between chorea and pericarditis in proper perspective. Begbie[5] was a firm believer in the rheumatic nature of chorea, and discussed the matter at great length in a communication which he read to the Medico-Chirurgical Society of Edinburgh in 1847. He showed from his own clinical experience and that of his colleagues that chorea and rheumatism may 'occur conjointly or severally in different individuals of the same family.' He described one family in which the father had rheumatic fever, and at the same time his eldest child, a girl of 5 years, was suffering from a severe attack of chorea. Later the father again had rheumatic fever and the girl, without any subsequent chorea or arthritis, developed an advancing endocarditis of the mitral valve from which she died. In another family of 9 children, a girl of $12\frac{1}{2}$ years had chorea, a younger sister also at $12\frac{1}{2}$ years developed chorea; later on a brother at the age of 18 suffered from rheumatic fever with pericarditis; and still later the younger girl had an attack of typical rheumatic fever followed by endocarditis, and during convalescence a second seizure of chorea. In the third family, in which the mother had had acute rheumatism after her first delivery, a boy of 13 had chorea supervening on a second attack of arthritis; an elder brother, after several attacks of rheumatic fever and one of chorea, developed aortic endocarditis; and a sister at the age of 17 years had chorea. From these family histories the conviction of the identity of the rheumatic nature of chorea, arthritis and carditis was forced on Begbie and he wrote;—

> I cannot help coming to the conclusion that the simple and true view of their relation is to be found in the morbid condition of the blood which is admitted to exist in the rheumatic constitution; and this explanation will apply equally to chorea occurring in individuals or

families inheriting the rheumatic diathesis—to chorea occurring in connection with rheumatism but without cardiac complication—and to chorea associated with pericarditis or endocarditis or both; the inflammatory affection of the fibrous tissues, as well as the spasmodic affection of the muscles, and the derangement of the nervous system, originating in the same specific disorder of the circulating fluids.

His prophesy that 'the labours of the microscope and the progress of organic chemistry, may ere long reveal to us in what this disorder consists' has unfortunately, however, not been fulfilled even now almost 100 years later.

One would have thought that a clinician of Graves's acumen would have had something to say on this matter, but in his famous Lectures on Clinical Medicine published one year after Begbie's communication there is not a single reference to any association between chorea and pericarditis. It is questionable, however, if Graves had any idea of the relationship between chorea and rheumatism, although he was quite definite concerning the part played by the latter infection in pericarditis. Nevertheless the teaching that chorea was rheumatic in nature thereafter gradually became accepted (Sée, Roger, Trousseau[23]). Chief interest, however, veered off from its association with pericarditis and became centred round the search for an explanation of the nature of the disturbance of the brain. Begbie gave no theory, probably because being a true scientist he saw no reason to justify him in suggesting any. The meningeal cause was discarded and the pericarditic origin of the irritation seemed too fantastic, as well as not being an invariable or even frequent accompaniment. Kirkes[24], who was quite decided that chorea was a rheumatic manifestation, pointed out that 'it allies itself with endocardial and not pericardial disease, and that whenever chorea occurred in connection with rheumatism the valves of the left chamber of the heart were inflamed, and therefore that the association is not between chorea and rheumatism but really between chorea and valvular disease of the heart.' From this association he developed the thesis that chorea was due to embolism of the very minute arteries in the brain, the source of the emboli being the vegetations on the valves. This explanation was adopted by Hughlings Jackson[26] who even specified the site of the embolism as the corpus striatum. The fact pointed out by Vogel[27], that while rheumatic carditis was more frequent in boys chorea was more frequent in girls, did not shake belief in this theory which held sway for many a day. Apparently in consequence of this new conception of the causation of chorea all interest in its association with pericarditis lapsed, and subsequent writers as Trousseau, Gairdner[28] and Radcliffe make no mention of it. In fact, Sir Thomas Watson[29] in his exhaustive lecture on pericarditis detailed at great length the nervous phenomena (convulsions, delirium and coma) which may accompany it, but made no single mention of chorea.

It would appear to be Sir William Osler[30] who resuscitated interest in our time in the association of pericarditis and chorea, since it is in his writings that one again first meets a reference to it. In his monograph on chorea published in 1895, pericarditis in chorea received individual consideration. He also recalled the work of Copland and Bright, and stated that 'in 19 of the 73 recent autopsies in chorea which I have collected' (we suppose he means from

the literature though he does not say so) ' pericarditis occurred as a complication, and in 17 it was associated with endocarditis. In 8 of the cases there was a history of acute rheumatism (arthritis). One case had subacute rheumatism, one rheumatic pains, while nine had not had acute arthritis.' The example of associated pericarditis and chorea which Osler quoted is not only not a striking one, but occurred in the practice of his colleague Sinkler who published it. The patient was a boy of 6 years who had arthritis in February, 1888, chorea in March, 1888,—the chorea continued for months—and an attack of typical pericarditis with effusion in January, 1889, by which time, however, the chorea had disappeared. Thus just as in the cases described by the earlier writers arthritis was again a precursor. This is also true of practically all recent writers. They all speak of chorea as being responsible for pericarditis, but all the illustrative cases of rheumatic pericarditis which they quote had all suffered from arthritis as well as chorea[31]. The only exception that we have come across is Nobécourt[31], who recorded two instances of pericarditis and chorea as the only manifestations of rheumatism. The one was a personal observation in a boy of 7 years who for 12 days had ' some pericardial rubs ' in addition to a well marked mitral systolic murmur. The other instance he quoted from Cadet and Gassicourt affecting a boy of 9 years in whom a well marked pericarditis with effusion occurred during a second attack of chorea, and in whose case there is no mention of him having suffered from arthritis. From our own cases (see appendix), and also from those of other writers quoted above, the very varying sequence in which the various rheumatic manifestations appear is so striking that one does not hesitate to believe that not only in the two cases recorded by us, if they had survived, but also if the subsequent history of the cases quoted by Nobécourt were known, an attack of arthritis would fall to be recorded.

Nobécourt in his treatment of the question remarked on the difference in the picture of pericarditis as observed in arthritis and in chorea. He said that pericarditis in association with chorea is occult and does not reveal itself by symptoms or signs except occasional friction rubs at the base of the heart. The examples, however, which have come under our observation, details of which are supplied in the appendix, do not support any such conclusion. In all of the 15 cases in which the pericarditis was present during the course of chorea the cardiac condition was severe, and death resulted in 10.

Conclusion.

It would thus seem that although pericarditis may very occasionally occur as the sole manifestation of rheumatism, or during the course of an attack of chorea, or even, but still more rarely, in an individual who has never had any other rheumatic manifestation than chorea, the association of pericarditis and chorea is anything but close, and, so far as rheumatism is concerned, arthritis is the almost invariable precursor or accompaniment of pericarditis. It was Kirkes who said that chorea and endocarditis, and not chorea and pericarditis, are allied ; and we would say it is arthritis and pericarditis which are

related. The fact that they are both examples of inflammation of a serous sac would make it exceedingly likely that there would be this relationship, but the immunity of the pleura, the peritoneum, and the pia-arachnoid to the rheumatic infection prevents us from pushing this analogy too far.

But in our opinions, to speak of either arthritis or chorea being responsible for pericarditis engenders a totally wrong conception of the rheumatic infection, and in relating cause and effect is as untenable as the thesis propounded almost 100 years ago by Bright and Babington that pericarditis caused chorea. Pericarditis just as endocarditis, arthritis and chorea, and also rheumatic nodules, is a manifestation of the rheumatic infection—the one is not dependent on the other but these are the various seats of election for the development of the rheumatic reaction ; and, as we know only too well, they may, especially during childhood, with the possible exception of the nodules, appear in any sequence.

This is an experience which has been familiar to all writers on rheumatism (Copland, Bright, Churchill, Radcliffe). Begbie[5] saw its significance and in the words previously quoted has put the matter in its proper perspective. Within comparatively recent times Cheadle[3] in his classical article on rheumatism in childhood again has expressed the same view. Cheadle wrote ' sometimes an arthritis appears first ; in other cases an endocarditis ; now and again a chorea inaugurates the morbid series . . . they may follow any order of sequence'; and further, when speaking of pericarditis, that it ' may arise at any step in the rheumatic series : first or last ; alone or combined with any one or more of the other manifestations such as endocarditis, arthritis, the evolution of nodules or chorea.'

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APPENDIX.

No. 13. J.K., male, 5 years. Admitted to hospital 29/12/19. Chorea 8 weeks and arthritis 6 weeks previously. Admitted with chorea. V.S. mitral murmur, nodules on elbows and knees but no evidence of arthritis. 3 weeks after admission, fever and pericardial friction. Died suddenly 3 months after admission. At P.M. examination pericardium obliterated by œdematous fibrous tissue, no free exudate, recent vegetations on mitral valve.

No. 27. J.McF., female, 5 years. Came under observation 15/2/18 with fever and dyspnœa of 3 weeks' duration. Father had had rheumatic fever 7 years previously. Admitted with fever, dyspnœa, slight chorea of right arm and leg, pericardial effusion and friction, and V.S. mitral murmur. Died suddenly 3 days after admission. At autopsy bread and butter pericardial exudate, and extensive endocarditis of mitral valve.

No. 26. N.C., female, aged 10 years. Admitted to hospital 12/10/20. 3 weeks previously erythema nodosum; 2 weeks later chorea with pains in ankles and knees which were swollen. On admission temperature 101°, severe generalized chorea, swelling of both knee joints, right tender, heart enlarged with V.S. mitral murmur. Fever continued, cardiac dullness became pyramidal in shape extending as high as second rib with muffling of sounds but no friction. Chorea subsided somewhat, but child got weaker and died suddenly 8 days after admission. At P.M. examination old and recent pericarditis, and endocarditis of aortic and mitral valves.

No. 18. E.McC., female, 12 years. Admitted to hospital 13/7/25. History of chorea for 1 month, then 2 weeks, later dyspnœa and cardialgia; 2 days before admission swelling and pain in left ankle joint. On admission temperature 100·2°F., slight chorea of right leg and arm, swelling of left ankle; child cyanosed, fingers clubbed, great increase in area of cardiac dullness in all directions, loud pericardial friction, V.S. mitral murmur, dullness to percussion and moist râles at both bases. Died suddenly 18/7/25. No P.M. examination permitted.

No. 20 E.W., female, 11½ years. Admitted to hospital 29/11/23. 2 years previously, after a severe wetting, acute rheumatic fever and confined to house for several weeks. Soon after returning to school developed chorea, treated in Glasgow Royal Infirmary for 3½ weeks and at this time V.D.H. diagnosed. Remained well afterwards without any symptoms of cardiac disability till 1 week before admission, when complained of pain and stiffness of legs and also

left arm and shoulder. 2 nights before admission epistaxis and vomiting, pains worse and definitely fevered. On admission very ill, no fever, marked cyanosis and orthopnœa, heart dullness increased in all directions, loud widespread pericardial friction, V.S. mitral murmur. Died 2/12/23. P.M. examination refused.

No. 43. J.S., female, first came under observation at the age of 6 years with history of flitting pains in knees and ankle joints of 6 weeks' duration. 5 weeks before admission movements of legs and face, 2 weeks later erythema nodosum over both shins. Pains in legs had persisted. On admission no fever, moderately severe chorea, no tenderness or swelling of joints, heart not enlarged but V.S. murmur audible at apex; during this period in hospital mitral stenosis and regurgitation diagnosed. Child seen again at age of 8 years with recurrence of chorea and signs of mitral stenosis and regurgitation: remained in hospital 5 weeks by which time chorea had disappeared. 3 months later admitted to East Park Home for Children under the care of Dr. A. Bankier Sloan: 3 months after admission to East Park Home she developed well marked acute pericarditis and died. No P.M. examination performed.

No. 21. E.B., female, came under observation at the age of 7 years on 7/11/26 with a history that for a nasal discharge of some considerable duration: tonsils and adenoids had been removed 18 months previously. 4 months previously had been in bed for 3 weeks with rheumatic fever and doctor in attendance said that heart was affected. 2 months ago chorea. 5 days before admission sore throat with headache, vomiting and fever followed by dyspnœa 4 days later. On admission fever, 102·4°, rapid breathing (56 per min.), heart enlarged in all directions, V.S. mitral murmur and loud to-and-fro pericardial friction. Fever subsided within 3 or 4 days, friction disappeared. Child gradually improved and was dismissed with heart enlarged and a loud V.S. mitral murmur.

No. 41. M.McQ., female, admitted to hospital 28/10/27. In early childhood tubercular adenitis. 2 weeks before admission pain and swelling of ankles and knees, and 2 days before admission jerking movements of right arm and face. Admitted at age of 10½ years with fever (temperature 101·8°), slight swelling of left wrist joint, slight chorea of right hand and enlargement of heart with V.S. mitral murmur. Fever and swelling disappeared within 1 week but chorea persisted. Fever returned during 3rd week of residence in hospital, cardiac dullness increased upwards and over the heart, in addition to V.S. murmur, to-and-fro pericardial friction was audible. Fever subsided somewhat in 10 days and friction became less marked, but chorea persisted, and nodules appeared on elbows and knees. She suddenly became seriously ill, was dyspnœic, developed an irritating cough with profuse frothy bright red sputum and died about 6 hours later. No P.M. examination permitted.

No. 23. J.W., female, 6½ years. Admitted to hospital 19/5/28. Came under observation with history that 2 days previously had become fevered and had developed pain and swelling in left ankle and knee. Admitted with temperature 100·4°, pain and swelling of left ankle and knee, erythema marginatum on abdomen and back, very slight chorea, and enlargement of heart with a mitral systolic murmur. 3 days later increase in fever (103°), pain in joints had gone (probably in response to salicylates); cardiac dullness, however, still further increased, especially upwards, and loud pericardial friction was heard in addition to V.S. murmur at apex; very slight chorea. Fever persisted for 3 weeks, pericardial effusion became extreme. On aspiration of pericardium there was obtained a blood-stained fluid the cellular elements of which were, in addition to red cells, entirely polymorphonuclear cells. Pleural effusion developed at end of febrile period and revealed characters of passive exudate. Child gradually improved and was dismissed with heart enlarged and V.S. mitral murmur.

No. 14. L.S., female, first seen at the age of 5 years with history that 4 months previously had had scarlet fever, and that shortly afterwards there had appeared jerky movements of left hand extending later to right; no history of joint pains. Admitted with severe generalized chorea and a V.S. mitral murmur. Treated with antipyrine for 1 week, isolation for 3½ weeks and then with liq. arsenicalis, min. xv, t.i.d., for 1 week, but chorea persisted. At this period fever developed and 4 days later acute pain in hip appeared. With salicylates pain in hip

disappeared and finally subsided. Chorea disappeared 2 months after admission to hospital, and child was dismissed after 3 months residence. Child again came under observation 3 months after dismissal with cardialgia, dyspnœa amounting to orthopnœa. Examination revealed enlargement of heart to right and left, with V.S. mitral murmur and pericardial friction, no great effusion.

No. 25. B.McC., female, came under observation at age of 12 years on 24/6/25. History of occasional growing pains; chorea at 8 years. 2 weeks previous to admission sore throat, in bed for a few days then allowed up, was dyspnœic and ultimately orthopnœic, requiring two pillows, and developed pain in chest and choreiform movements in right arm and leg. On admission temperature 103°, slight chorea in right hand, cyanosed, orthopnœa, cardiac dullness pyramidal in shape extending to clavicle, course pericardial friction, A.S. and V.S. mitral murmurs, dullness at both pulmonary bases with tubular R.M. and râle. Fever disappeared within 3 days but child's general condition did not improve, ascites and œdema of feet appeared and child died somewhat suddenly 7 days after admission. At P.M. examination old and recent pericarditis, mitral cusps thickened (orifice 1·1 inches), hypostatic pneumonia at both bases, hypostasis of liver, spleen and kidneys.

No. 42. M.McG., female, came under observation at age of 9 years with history that 2 months previously, 6 weeks after scarlet fever, she developed attack of polyarthritis, and that with treatment all pain and swelling of joints disappeared. Two weeks before coming under observation chorea appeared. On admission, severe chorea with paresis of left arm and leg and loud blowing mitral systolic murmur. During her residence at this time she suffered from arthritis and chorea synchronously, but they alternated somewhat in that when the chorea was most severe the arthritis was least painful and vice versa. Her mother and an elder sister had both died of rheumatic cardiac disease. Child again came under observation at the age of 10½ years on account of increasing dyspnœa on exertion which had troubled her since her dismissal from hospital. The heart at this time was greatly enlarged and there was evidence of mitral and aortic disease. She improved somewhat and was dismissed home, but returned again 2 weeks later. She again improved with residence in hospital but developed chicken-pox and was transferred to an isolation hospital. She was admitted for the last time at the age of 11½ years with another attack of arthritis, V.D.H. implicating both mitral and aortic orifices and decompensation. After 2 weeks pericarditis ensued as evidenced by loud friction, and child died 1 month after admission. At autopsy old and recent pericarditis, old endocarditis of both mitral and aortic cusps with much puckering, and in addition recent vegetations on the aortic cusps.

No. 47. A.D., female. History of mild attack of chorea at 9 years and heart at this time said to be affected. Came under observation at the age of 11 years and 2 months on account of pain over præcordia and dyspnœa of 10 days' duration. Onset sudden with cough and feeling cold and vomiting with rapid development of pain over chest and dyspnœa. On admission fever (temperature 102·7°). Evidence of pericarditis in pyramidal-shaped dullness and loud friction: endocarditis with A.S. and V.S. murmurs and pleural effusion at left base and hæmorrhagic nephritis (blood and casts in urine). Left pleura explored and clear serous fluid withdrawn revealing polymorphonuclear cells and pneumococci. Pericardium explored but only blood obtained Child died 3 weeks after admission. No P.M. examination was permitted.

No. 49. E.T., female, first seen at age of 6 years with typical chorea; heart not affected. Her maternal aunt had chorea during childhood and has V.D.H. At 8 years child had another attack of chorea and was again in hospital: heart still free. At age of 9 years an attack of subacute rheumatic fever followed by another spell of chorea for which admission to hospital was again necessary, and at this time mitral disease diagnosed. When 10½ years old fourth attack of chorea, by which time mitral stenosis and regurgitation were present; shortly afterwards slight swelling and pain and tenderness of ankles. At 11 years admitted to hospital once more with a story of præcordial pain, dyspnœa and fever of 1 week's duration. On admission temperature 101°, great enlargement of area of præcordial dullness, pericardial friction, A.S. thrill with A.S. and V.S. mitral murmurs. Shortly after admission pericardium aspirated; 40 c.cm. very

slightly blood-stained serous fluid withdrawn which on centrifugalising gave a deposit consisting of lymphocytes, polymorphonuclear and endothelial cells; no organisms seen and no growth obtained on culture.

No. 46. G.C., male, had attack of chorea at age of 3½ years, and again at age of 4½ years when he was under our observation and at this time mitral disease was diagnosed. At the age of 6½ years he had his third attack of chorea with at the same time pains in all his joints and over the heart. On admission to hospital there was fever 101°, moderately severe chorea, nodules on elbows and malleoli and spinous processes of vertebral column; enlargement of area of cardiac dullness with mitral systolic murmur and pericardial friction, moderate effusion. Child gradually improved, nodules disappeared as also did pericardial friction.

CALCIUM AND PHOSPHORUS METABOLISM IN SOME OLDER CHILDREN ON MIXED DIET INCLUDING A LARGE OR A SMALL QUANTITY OF MILK

BY

ANGELIA M. COURTNEY, B.A., and ALAN BROWN, M.B.

(From the Sub-Department of Pædiatrics, University of Toronto, and the Hospital for Sick Children, Toronto.)

In view of the frequently observed stimulating effect on growth of large amounts of milk included in the mixed diet of older children, it was thought worth while some years since to determine the calcium and phosphorus excretion and retention during periods of feeding with high milk and low milk diets. The observations were completed shortly before the appearance of the valuable contribution by Sherman and Hawley[1] on calcium and phosphorus metabolism in childhood. Our results seemed not altogether consistent, and as Sherman and Hawley's work covered the ground far more completely than ours, these results were set aside for the time.

A recent consideration of the data has revealed some interesting relationships among groups of the children studied, and the findings seem to have a more instructive aspect than was at first apparent.

Beyond demonstrating clearly that the low milk diets contained too little calcium and phosphorus to provide for retention of those elements, at least during the period of observation, there were no clear cut differences in the findings for the two dietary groups, that on a high milk and that on a low milk mixed diet. On the contrary, the values found for each dietary group fall into two distinctly different classes, making altogether four groups of two children each, and in each group the calcium and phosphorus metabolism appears to be strikingly similar for the two making up the group, while distinctly different from that of the other groups. An account of the conditions of the study will precede a discussion of the findings.

The subjects of the study were two girls, respectively 5 years and 10 months, and 6 years and 2 months, and two boys, 9 years and 5 years, who were given a suitable mixed diet, modified to include a large amount of milk, partly in cooked items of the diet, partly given as drink ; also two girls, 5 years and 10 months, and 9½ years respectively, and two boys 8 years and 2 months and 13¼ years, who were given a mixed diet containing very little milk, but suitable as regards caloric value and percentage composition. The girls were all surgical cases recovered after treatment for congenital disclocation of the hip or infantile paralysis. One in the pair forming Group 4 was somewhat underweight. The

boys were of various conditions: one somewhat underweight after recovery from tuberculous glands, one a mental defective physically normal, one an epileptic free from attacks at the time of observation, fairly well-nourished and with normal sugar tolerance, the fourth a congenital syphilitic undersized but in fairly good condition at the time. Serum calcium and phosphorus were determined in seven of the eight children and were in all cases normal.

The four girls were under observation together, two on each kind of diet, and immediately after the four boys were studied under practically the same conditions as the girls. The corresponding menus for girls and boys were as nearly as possible the same. A variation in kind of cereal, vegetable, meat and cooked fruit was made from day to day in accordance with hospital routine with both boys and girls. The high milk diet was as follows:—

Breakfast: Orange, cereal, sugar, milk, bread and butter.
Dinner: Cream soup, potato, one other vegetable, custard, milk.
Supper: Cereal, sugar, milk, junket, bread and butter.

This diet included 32 ounces of milk besides that in cream soup, custard, and junket. The girls in Group 1 refused part of the milk and cream soup, and both boys refused part of the cream soup.

The low milk diet was as follows:—

Breakfast: Orange, cereal, sugar, milk, bread and butter, lemonade.
Dinner: Meat, potato, another vegetable, jelly, orangeade.
Supper: Egg, cooked fruit, bread and butter, lemonade.

This diet included only four ounces of milk, taken with the cereal at breakfast. The weather being warm the fruit juices were an acceptable substitute for milk. On both diets the boys usually took more bread and butter than the girls. The wide difference in the two diets in milk content necessitated making important differences in the other items, particularly in order to bring up the protein and fat content of the low milk diet. With all modifications practicable, the fat intake on the low milk diet was much lower than on the high milk one, for the children on low milk intake would not take the extra butter offered, while those on high milk intake would not take skim milk. Obtaining ideal experimental conditions was made secondary to giving diets which would be taken with appetite and no undue urging. This was especially difficult as the children had been for some time in hospital, took little exercise and the weather was warm and debilitating.

The children were given their respective diets for a short preliminary period. The exact measurement of the intake was carried out for five days, and a representative sample corresponding to the food taken by each child was reserved for four days to make up a composite collection for the period of analysis. The separate collection for each child was necessary because of slight, or in one case considerable, variation in the amounts taken. Fæces and urine were collected in twenty-four hour quantities, the fæces for the first day and urine for the fifth being discarded. When it seemed necessary in order to insure a regular excretion of fæces, a plain water enema was given. The analyses of urine and fæces were made on composite samples for each child. Standard gravimetric methods for determining calcium, magnesium and phosphorus were

used. Fat was estimated by a modification of the Roesse-Gottlieb method. No changes in physical condition of the children were noted during the observation period.

The findings have been arranged in two tables giving values for intake and fæces content of fat, calcium, magnesium and phosphorus, and urinary and fæcal excretion and retention of calcium and phosphorus. The children are classified in these tables in four groups, 1 and 2 on the high milk diet, and 3 and 4 on the low milk. On the high milk intake one girl and one boy form one group and the other boy and other girl another group, the two of each group showing similar conditions of excretion and retention of calcium and phosphorus. On the low milk diet the two boys form one pair and the two girls another pair, the two of a pair showing similar metabolism of calcium and phosphorus. Except in Group 1 the intake of the two children of a group corresponds fairly closely. In Group 1 the girl had a poor appetite and took considerably less milk than the other children on the high milk diet. The girls forming Group 4 took slightly less food than the boys on the same diet.

The question arises whether the different assimilation of calcium and phosphorus by these children on similar diets can be explained by differences in their condition of health.

The girls were all surgical cases, well-developed and well-nourished, except Hilda, who was thin and somewhat emaciated. Agnes had been receiving treatment for infantile paralysis, the other three for congenital dislocation of the hip. There is more reason to consider three of the boys not quite normal, though none was ill at the time. Tommy had recovered from tuberculous glands but suffered from endocarditis and mediastinal tuberculosis and was underweight. Ivan was an epileptic but had been without seizures for a considerable period. He was well-nourished. Billy was a congenital syphilitic and had paroxysmal hæmoglobinuria, but though thin and undernourished, was well at the time, not having had a chill for more than a month. Abe, the fourth boy, was mentally subnormal but physically normal.

The theory might be advanced that the intake of Regina in Group 1 was more nearly ideal than the greater intake of the other three children on the high milk diet, but that under-nourished and tuberculous Tommy needed and assimilated the larger intake, the normal Abe and Agnes did not. This reasoning, however, cannot be applied to Groups 3 and 4, as one of each of these groups was distinctly better nourished than the other, but the diet of the two of each pair was almost identical.

Discussion.

Groups 1 and 2, on large calcium and phosphorus intake :—The calcium intake is larger than Sherman and Hawley's[1] estimate of the requirement of children, 1 grm. calcium a day, equal to 1·4 grm. calcium oxide; but neither the intake of calcium nor that of phosphorus can be considered excessive, according to the study of Orr and his fellow-workers.[2]

Group 1 shows a much smaller excretion of both calcium and phosphorus in the fæces and in urine than Group 2 ; a much greater retention of calcium

and of phosphorus, than Group 2; and about the same excretion of phosphorus in fæces and in urine or more in urine.

Group 2 shows greater excretion of fat and total salts as well as of calcium and of phosphorus than Group 1, and greater excretion of phosphorus in fæces than in urine.

Groups 3 and 4, on low intake of calcium and of phosphorus, extremely low of calcium :—

Group 3 shows a much smaller excretion of calcium in the fæces and distinctly less of phosphorus than Group 4; less calcium in the urine but very much more phosphorus in the urine than Group 4; a near equilibrium as to retention of calcium and slight negative balance of phosphorus; and more phosphorus in urine than in fæces.

Group 4 shows a large negative balance of calcium and smaller of phosphorus; and more phosphorus in fæces than in urine.

The difference in calcium and phosphorus metabolism between Groups 3 and 4 on low intake of calcium and phosphorus seems to be more or less parallel with that between Groups 1 and 2 on the high intake, but there is a striking difference between the high and low groups in respect to excretion of phosphorus in the urine. Group 4 on the low intake with greater fæcal excretion of phosphorus shows greatly reduced urinary excretion, while Group 3 has much more in the urine than in the fæces. On the other hand on the high intake, in Group 2 with greater fæcal excretion of phosphorus than in Group 1, there is also greater urinary phosphorus excretion.

In the entire lack of data concerning acidity conditions, particularly total excretion of acids and bases through fæces and urine, an attempt to explain these differences in calcium and phosphorus metabolism on practically the same diet is mainly theorizing. It is advanced by several writers, among whom may be mentioned Telfer[4], Orr[2], Chaney and Blunt[5], and Bergeim[6], that too little acid in the beginning of the small intestine interferes with absorption of the calcium and phosphorus of the intake, particularly of the calcium, and as a result calcium and phosphorus pass into the large intestine as insoluble calcium phosphate. That this is not the whole story is evident from the condition shown in Groups 3 and 4, where in the one group the fæcal calcium is nearly equal to the entire intake of calcium and in the other group far surpasses that of the intake. In these two groups, especially in Group 4, there must have been a considerable excretion of calcium into the large intestine from the body. Some studies on the intestinal contents of rats made in this laboratory[3] indicate that calcium is largely absorbed from the small intestine and excreted into the large, into the cæcum in the rats.

That fat excretion and need of calcium for formation of calcium soaps plays a small part in cases of excessive calcium excretion in the fæces is well shown in Table 1. The highest fat excretion was in Group 2. Allowing for a considerably greater proportion of soap fat in Group 2 than in Group 1, at the most the difference in soap fat excretion between Groups 1 and 2 could not have been as great as 2 grm., and probably was far less than that. Two

TABLE 1.

COMPOSITION OF FOOD AND OF FÆCES. DAILY AVERAGE.

Group	Food								Fæces						
	Total solids grm.	Fluid intake oz.			Total fat grm.	CaO grm.	MgO grm.	P_2O_5 grm.	Total solids grm.	Protein calc. from N. grm.	Total fat grm.	Total ash grm.	CaO grm.	MgO grm.	P_2O_5 grm.
		Milk & cream soup	Fruit juice bev.	Water											
1															
Tommy ...	370	35½	—	8½	72	2·199	·429	3·316	11·9	3·16	1·80	2·78	1·224	·170	·860
Regina ...	276	30	—	8	54	1·616	·285	2·417	14·3	4·04	2·49	3·17	1·115	·163	·769
2															
Abe	389	36	—	11½	76	2·308	·376	3·422	25·0	7·30	3·97	5·53	2·022	·235	1·618
Agnes ...	334	35½	—	6	72	2·237	·389	2·874	17·6	4·97	3·82	4·51	1·922	·273	1·562
3															
Ivan ...	343	5	24	11	43	·634	·292	1·465	17·6	5·60	1·86	2·30	·590	·159	·634
Billy ...	338	5	24	11	44	·622	·232	1·591	24·2	6·94	2·76	2·64	·401	·302	·573
4															
Hilda ...	203	4	13	8	27	·481	·174	1·041	14·7	5·11	2·04	3·18	·904	·136	·892
Evelyn ...	266	4	18½	8	30	·467	·196	1·078	15·2	4·96	2·11	3·11	·993	·132	·868

TABLE 2.

EXCRETION AND RETENTION OF CALCIUM AND PHOSPHORUS. DAILY AVERAGE.

Group	Excretion in urine		Ratio fæcal to urinary excretion of P_2O_5	Sum of CaO, MgO & P_2O_5 excretion in fæces*	Excretion in fæces and urine				Retention			
					CaO		P_2O_5		CaO		P_2O_5	
	CaO grm.	P_2O_5 grm.		grm.	grm.	% of intake	grm.	% of intake	grm.	% of intake	grm.	% of intake
1												
Tommy	·105	1·050	·82	2·25	1·33	60·3	1·91	57·6	·871	39·6	1·407	42·4
Regina	·069	·069	1·08	2·05	1·18	73·1	1·48	61·2	·431	26·7	·935	38·7
2												
Abe	·170	1·294	1·25	3·87	2·19	95·0	2·91	85·1	·116	5·0	·511	14·9
Agnes	·259	1·091	1·43	3·76	2·18	97·5	2·65	92·3	·056	2·5	·221	7·7
3												
Ivan	·081	·920	·69	1·38	·671	106·1	1·55	106·1	·037	—	·089	—
Billy	·157	1·135	·50	1·28	·558	89·8	1·71	107·3	·063	10·2	·118	—
4												
Hilda	·088	·370	2·41	1·93	·992	206·3	1·26	121·3	·512	—	·222	—
Evelyn	·230	·491	1·77	1·99	1·22	261·8	1·36	126·0	·755	—	·281	—

grammes of soap fat would require only about 0·2 grm. of calcium oxide to form soap, which amount is seen to be insignificant in comparison with the large difference in calcium excretion between Groups 1 and 2.

The large urinary excretion of phosphorus in Group 3 is difficult to understand in company with so small an intake of phosphorus, especially when resulting in a slight negative balance. However, the greater intake in Group 3 than in Group 4 made it possible to allow an ordinary urinary excretion in Group 3 and yet hold practically phosphorus equilibrium, while in Group 4 the lower intake and greater fæcal output were accompanied by greatly reduced urinary excretion as well as phosphorus deficit.

Summary.

1. Two boys and two girls were fed mixed diets including a large quantity of milk, and two other boys and two other girls a corresponding diet containing very little milk. Food, urine and fæces were collected quantitatively for four day periods and analysis were made for fat, calcium, magnesium and phosphorus in order to determine the excretion and retention of these constituents.
2. The low milk diets, even with inclusion of eggs and vegetables, were found to provide far too little calcium and phosphorus for the necessary retention of these elements.
3. The results were found to fall into two distinct groups for each kind of diet. In one group on each calcium and phosphorus level the excretion of calcium and phosphorus, except urinary phosphorus, on the low intake, was much less than in the other on the same diet and the retention correspondingly better. The large urinary excretion of phosphorus in Group 3 is difficult to explain.
4. These observations afford evidence that children on the same diet and apparently in equally good condition can on occasion differ so materially in their metabolic processes that one may lose through the fæces far larger amounts of calcium and phosphorus than the other, even to the point of suffering a serious loss to the body when the intake of these elements is low.

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SOME STUDIES ON CALCIUM AND PHOSPHORUS CONCENTRATION IN THE SMALL AND LARGE INTESTINES OF CHILDREN

BY

ANGELIA M. COURTNEY, B.A.

(From Sub-Department of Pædiatrics of the University of Toronto, and the Hospital for Sick Children, Toronto.)

This study was undertaken in the hope of obtaining some knowledge of excretion and absorption of calcium and phosphorus in the intestinal tract beyond that afforded by balance experiments and examination of the fæces.

The material investigated was obtained from thirty-four post-mortem examinations of the intestinal tract of children. It was out of the question to make much selection of cases for study. They were obtained over a period of thirteen months and represent as regards the intestinal tract both normal and pathological conditions. According to a classification based on the clinical and post-mortem reports, in twenty-one cases intestinal conditions were primarily normal; in fourteen definitely pathological. In thirteen cases signs of active rickets were reported, eight in the group showing acute intestinal symptoms. The group normal as to intestines included cases of decomposition, prematurity, broncho-pneumonia, erysipelas, nephritis, cellulitis, encephalitis, meningitis, hydrocephalus, scurvy, hæmorrhagic disease of the new-born and cerebral hæmorrhage following injury. The gastro-intestinal cases were described as acute intestinal intoxication, fermentative diarrhœa, one pyloric stenosis, one intestinal obstruction. The ages ranged from twelve days to four and three-quarter years, with the larger number between two months and one year.

The post-mortem examinations took place from two to twenty-four hours after death, the greater number within twelve hours. The material was, with few exceptions, used immediately after removal from the intestines. When this was not the case, it was kept covered in an ice-box and used as soon as possible. When there was sufficient material and it could be used at once, the moist material was made into an emulsion and a portion was used for hydrogen-ion determination. The remainder was dried to constant weight on a steam-bath in order to afford a basis for calculating the values as percentage of total solids. Calcium and phosphorus were determined in the dried material by standard gravimetric methods. When the material could not be used at once, or there was little obtained, the reaction was tested in the moist substance by the use of litmus paper and all was dried to constant weight to be used for the calcium and phosphorus estimations. When material permitted, chloride was estimated in the dried substance.

With three exceptions the intestinal contents were collected in two portions, all the material between the pylorus and the ileo-colic valve, and all that after the ileo-colic valve. In three cases only was it possible to collect separately the contents before the ileum and the contents of the ileum. A strictly quantitative removal of the contents was not attempted owing to the difficulty encountered in obtaining the material without admixture of blood. Accordingly the values reported represent concentrations, not the absolute amounts present. The total values would, however, have no significance here since no relation to the food intake was known.

Table 1 gives the average values for calcium and phosphorus concentration in the small and in the large intestine for all the cases. These cases are in addition classified in three groups, those with and those without intestinal symptoms, and those showing signs of rickets whether in the intestinal or in the non-intestinal group, and the averages for these groups are given in Table 1. Table 1 also includes the ratio of the concentration in the large to that in the small intestine of both calcium and phosphorus for each of the groups.

TABLE 1.

AVERAGE CONCENTRATION OF CALCIUM AND PHOSPHORUS IN SMALL AND LARGE INTESTINES IN GRAMMES PER GRAMME OF TOTAL SOLIDS.

	CaO					P_2O_5				
	1. Small intest.		2. Large intest.		Ratio 1 : 2.	1. Small intest.		2. Large intest.		Ratio 1 : 2.
	No. Cases	Aver.	No. Cases	Aver.		No. Cases	Aver.	No. Cases	Aver.	
Total number	34	·0149	30	·0371	2·5	32	·0293	23	·0452	1·5
Not intestinal	20	·0183	19	·0466	2·5	19	·0315	15	·0544	1·7
Intestinal ...	14	·0101	11	·0205	2·0	13	·0261	8	·0279	1·1
Rachitic ...	12	·0135	11	·0324	2·4	11	·0268	8	·0510	1·9

The following points are shown in this table :—

1. In all three groups calcium concentration in the large intestine is markedly greater than in the small.

2. Phosphorus concentration is definitely greater in the large intestine than in the small except in the group with intestinal symptoms.

3. The ratio of concentration in the large to that in the small intestine is much greater for calcium than for phosphorus.

4. With the intestinal cases the ratio of both calcium and phosphorus concentration in the large to that in the small intestines is much smaller than with the cases without intestinal symptoms. In other words the concentration in the large intestine more nearly resembles that in the small in the abnormal intestinal conditions, in most of which there was increased peristalsis.

5. In the rachitic group the ratio of phosphorus concentration in the large to that in the small intestine is greater than the average for all the cases. This difference is not sufficiently marked to afford a basis for discussion, particularly as the stage of healing of the rickets was not known in any of the cases.

Table 2 gives averages of the same values used in Table 1 but here classified according to the reaction of the material. For this purpose hydrogen-ion concentration more acid than pH 6·8 were considered acid, those from pH 6·8 through pH 7·0 neutral, and those more alkaline than pH 7·0 alkaline. This more or less arbitrary basis was fixed upon as giving the best agreement with the litmus paper tests. This table calls for little comment. The values for the acid and alkaline groups show the expected relationship, greater concentrations of calcium and phosphorus corresponding to alkaline reactions. The values for the neutral group are of less significance as the group was so small.

Only general conclusions can be drawn from these averages, for the individual values making up each average show a fairly wide range. There were, however, only two exceptions to the rule that calcium concentration is greater in the large than in the small intestine. In these two, total ash and phosphorus concentration also were less in the large intestine. In six instances the phosphorus concentration was less in the large than in the small intestine, though in all these the concentration of calcium was as usual greater in the large. In all but one of these the contents of the large intestine were distinctly acid, in four of them more acid than in the corresponding small intestine. As inorganic phosphorus was not estimated by itself no assumption can be made as to what proportion of the calcium present was bound to phosphorus.

TABLE 2.

AVERAGE CONCENTRATION OF CALCIUM AND PHOSPHORUS IN SMALL AND LARGE INTESTINES IN GRAMMES PER GRAMME OF TOTAL SOLIDS.

	Small intestine			Large intestine		
	No. cases	Average	Range	No. cases	Average	Range
CaO						
Total number ...	34	·0149	·0020—·0515	30	·0371	·0056—·1463
Acid reaction ...	31	·0135	·0020—·0298	18	·0300	·0056—·0781
Neutral „ ...	1	·0188		4	·0256	·0083—·0438
Alkaline „ ...	2	·0346	·0176—·0515	8	·0587	·0100—·1463
P_2O_5						
Total number ...	32	·0293	·0069—·0486	23	·0482	·0158—·1384
Acid reaction ...	29	·0289	·0069—·0449	13	·0388	·0158—·1034
Neutral „ ...	1	·0237		3	·0408	·0318—·0491
Alkaline „ ...	2	·0365	·0244—·0486	7	·0588	·0270—·1384

Table 3 gives the average chloride values for the small number of estimations made, arranged in groups corresponding to those in Table 1. The number making the averages is too small to allow great importance to be attached to them. They are included because of the strikingly higher concentration of chlorides in the rachitic cases than in the others. This might be expected if the rickets happened to be in the healing stage with most of these cases, since it has been observed that in rats with healing rickets the contents of the large intestine are more watery than those of normal or actively rachitic rats[1], and it is also known that the sodium chloride content of fæces is increased with the water content.

TABLE 3.

AVERAGE CONCENTRATION OF CHLORIDES IN SMALL AND LARGE INTESTINES IN GRAMMES PER GRAMME OF TOTAL SOLIDS.

	Small intestine			Large intestine		
	No. Cases	Average	Range	No. Cases	Average	Range
Total number ...	17	·0218	·0107—·0407	7	·0107	·0031—·0299
Not intestinal ...	12	·0221	·0113—·0407	6	·0103	·0031—·0299
Intestinal	5	·0212	·0107—·0357	1	·0103	
Rachitic	7	·0300	·0113—·0407	2	·0208	·0116—·0299

The data obtained from this investigation are not extensive enough to justify drawing any definite conclusions as to absorption and excretion relations of calcium and phosphorus in the intestinal tract. However, since the ratio of phosphorus concentration in the large intestine to that in the small is distinctly less than the corresponding calcium ratio, it can fairly be concluded that these two constituents are not entirely interdependent in regard to absorption and excretion. This observation is in agreement with the findings in a study of the intestinal contents of rats recently made in this laboratory.[1]

This difference between calcium and phosphorus in the relation of their concentration in the large and the small intestine must be due either to greater increase in excretion of calcium than of phosphorus in passing into the large intestine, or to relatively less absorption of calcium than of phosphorus. This greater excretion or less absorption of calcium in the large intestine in comparison with phosphorus is brought out in another way. Inorganic phosphorus values were not obtained, hence the proportion of calcium bound as phosphate cannot be calculated even in approximate terms. However, if only about half the total phosphorus present can be regarded as inorganic phosphorus, as we found to be the case in the study of rats just referred to, then Table 1 shows that in all children investigated calcium must have been present in the large intestine in considerable proportion in some other combination than as phosphate. In the small intestine this excess of calcium was not present,

Conclusions.

The results here reported indicate that there was greater excretion or less absorption of calcium than of phosphorus in the large intestine in all the children studied. It also appears probable that the calcium concentration in the large intestine was due in considerable proportion to calcium not bound to phosphorus.

In the children with abnormal intestinal conditions there was much less difference between the large and the small intestine in both calcium and phosphorus concentration than in those without intestinal symptoms.

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SALT CONTENT OF WOMAN'S MILK IN SOME CASES IN WHICH ITS USE WAS NOT BENEFICIAL

BY

ANGELIA M. COURTNEY, B.A., and ALAN BROWN, M.B.

(From the Sub-Department of Pædiatrics, University of Toronto, and the Hospital for Sick Children, Toronto.)

During a period of four successive years there is a record at the Hospital for Sick Children, Toronto, of ninety infants admitted suffering from tetany in a more or less severe form. Of this number twenty had been breast-fed to date, some of the older infants taking in addition a milk dilution and sometimes cereal and biscuit. Two others of the ninety had been exclusively breast-fed to within two weeks of admission, and eight more had been breast-fed for a period of six months or longer after birth, though on artificial feeding for a month or more preceding the attack. Thus one-third of the infants with tetany had been breast-fed to date or for a period of six months or more after birth. It seems not unreasonable to conclude either that the mothers' milks were abnormal in composition, or that under adverse conditions normal woman's milk does not afford sufficient protection against tetany.

It is customary when breast-fed infants are admitted to the hospital suffering from tetany, or showing marked signs of rickets without tetany, to discontinue breast feeding entirely. Since under these circumstances it is usually a simple matter to obtain a large representative sample of the mother's milk, it seemed advisable to make complete salt analyses of the milk in as many cases as possible in order to learn how nearly these milks showed values within the normal range. As far as possible the milk was collected under the supervision of a nurse in the infant ward, and in the other cases explicit directions for making the collection were given the mother. The aim was to get all the milk that could be expressed from both breasts until a total of twenty ounces or more was obtained, the period of collection not to exceed three days. Beginning and end milkings by themselves were particularly to be avoided. The samples were kept cold until collection was completed, and no milk was used for analysis in a curdled state or when the cream could not be shaken into a homogeneous mixture with the rest of the milk.

Occasionally infants showed other symptoms than those of rickets and tetany which were assumed to be related to their being fed at the breast. This assumption was made because no other explanation was apparent and because usually the symptoms entirely disappeared when the infant was changed on to artificial feeding. In all such cases also, when practicable, collection of the mothers' milk was made for analysis. Altogether there were thus obtained for analysis seventeen milk samples from mothers of infants suffering from rickets and tetany, and thirteen from women whose milk appeared not to agree with the infants as indicated by other symptoms, such as, convulsions, not tetany, vomiting, diarrhœa, failure to gain in weight.

If the collected sample was sufficiently large, fat was estimated according to Babcock and a nitrogen separation was made in the fresh milk. The bulk

of the collection was immediately measured and set on a steam bath to dry to constant weight. In the powdered dried milk, total ash, calcium, magnesium, phosphorus, chloride, potassium and sodium were determined according to standard gravimetric methods. The sodium and potassium separation was made by the cobaltinitrite method according to the procedure of H. H. Green[1]. There has been some criticism of the cobaltinitrite determination of potassium on the ground that the precipitate of sodium potassium cobaltinitrite is not a strictly constant compound. The values obtained by this procedure are given for what they are worth, but because of their possibly questionable value there are also included in the table values for total sodium and potassium chloride as separated from the other salts before the determination of potassium was made. It must be kept in mind that these values being chlorides of the elements are large in comparison with the total ash values.

Table 1 gives the values in grammes per 100 c.cm. of milk for the salt analysis (A) of the milks of mothers of infants suffering from tetany or rickets, and (B) for the milks when the infants showed other symptoms supposedly related to the breast feeding. Table 2 was compiled from table 1 to bring out in a more graphic way a comparison of these values with the normal averages. Values are considered average, indicated by 'ave.', if very close to those obtained for mature milk by Holt et al[2]. In the case of CaO the average was considered to run to ·043 grm. per 100 c.cm. of milk because of the somewhat lower normal values found by Burhans and Smith[3] and by DeBuys and Meysenburg[4], and in the case of K_2O the average was extended to ·060 grm. per 100 c.cm. of milk, the value reported by Burhans and Smith. One (+) and one (—) was assigned to a value lying between the average and the normal limits for each element as given in Holt's tables, with a slight extension of the lower limit for calcium and the upper for potassium. For values higher or lower than the normal limits, the number of signs indicates the degree of divergence from the normal values. This distribution of signs is arbitrary but affords an approximately accurate measure of comparison of the different milks, particularly so in respect to each element by itself.

Considering table 2 as a whole it is seen that the greatest number of values outside the normal range, with more than one (+) or (—), occurs in the magnesium, chloride and sodium columns. In Group (A) alone sodium, calcium and magnesium have the greatest number of divergences, while in (B) all the columns except calcium and potassium show a large proportion of the values beyond the normal range. Thus it appears from these findings that the milks taken by the infants suffering from rickets and tetany show considerably less divergence from the normal in salt content than the milks which failed to agree with the infants for various other reasons. It is perhaps significant that in the rickets and tetany Group (A) the calcium and magnesium values, especially those for calcium, were mostly in the low direction from the average, though only about one-third were actually beyond the range found for normal milks. The values for phosphorus were more in the high direction, though few were beyond the normal range. The sodium column in this group shows many very high values in marked contrast with the calcium and magnesium values. This

is probably why the values for total salts were mostly in the normal range in this group. In Group (B) nearly all the values for total salts were higher than normal, for in Group (B) most of the abnormal values for the separate salts were in the direction of high values.

In four instances in which the milk calcium content was below the normal, values were obtained for the infants' blood calcium or phosphorus or both. In two of these both calcium and phosphorus of the blood were low, in one other calcium was low, phosphorus not being determined, and in the fourth calcium was normal but phosphorus very low, the infant in this case suffering from rickets only. In six other cases of Group (A) in which the milk calcium content was lower than the average but not beyond the normal limit, blood calcium or phosphorus or both were low.

The literature bearing upon the effect of diet upon the composition of the milk secreted was discussed in a preceding paper[5] in which four of the milk samples included in those here presented were reported, and the discussion will not be taken up again now. In connection with most of these milk collections a description of the diet of the mother was obtained, particular attention being given to the quantity of the milk taken and whether adequate sources of fat-soluble and other vitamines were included. Although these reports were not altogether satisfactory, on the basis of them an attempt has been made to classify the diets of the mothers represented in Group (A) as poor, if glaringly defective in quantity of milk and vitamin supply, fair if deficient in one of these respects but not the other, and very poor when total caloric intake as well as quantity of milk and vitamin supply were clearly below requirement. Of these mothers whose milk calcium content was below the normal limit the diets were in two cases rated very poor, in two poor, and in two fair. In four cases in which the milk calcium content was below the average but within normal limits, the diets of the mothers were rated poor. In no case was a diet of the mothers of the infants suffering from rickets or tetany rated above fair. Curiously one of the most deficient diets reported was that of the mother indicated (Case 16) in the table, whose values for milk salts were among those the most nearly normal in the Group (A). Nursing, however, had not been so long continued as in the majority of cases in the group, the infant being only four months of age. In most of the milks of Group (A) the fat content was lower than the average, in three cases abnormally low.

The cases in Group (B) require some individual discussion. Case 18, a six weeks' old infant, had convulsions which ceased on removal from the breast, the convulsions being considered not due to tetany. The milk was abnormally low in calcium and magnesium content. Case 19 also had convulsions not due to tetany, calcium content of the blood serum being normal. There was also an acute infection in this case. The concentration of milk salts was almost normal. Case 27, a two weeks' old infant with a temperature unaccounted for, was taking a milk almost lacking in magnesium and abnormally high in total salts, sodium and potassium. Case 28, an infant who was vomiting

when taking mother's milk, recovered when changed to artificial feeding. This milk had a magnesium and sodium content lower than normal, that of potassium higher. Case 25, a 3 months' old infant with eczema, was taking a milk abnormally high in total salts, magnesium, sodium and chloride. Cases 23, 20, and 22 designate milks of wet nurses supplying premature infants in hospital wards. The infants were not thriving or showing the progress expected under the circumstances. Analyses were not complete for two of these milks, but the only outstanding abnormalities found were a very high calcium content in one, and very high phosphorus content in another. With a three months' old infant not thriving on mother's milk (Case 24), the low fat content seemed to be sufficient reason for the failure to gain in weight. There was also a decidedly abnormal salt content, phosphorus, sodium and chloride all being extremely high. The mother took exceptionally large amounts of table salt with her food. In three other cases (21, 29 and 30), the infants had ceased to gain and suffered from diarrhœa while taking mother's milk, and improved when removed from the breast. All these milks had phenonemally high sodium, potassium, chloride and total salt content. In two cases sodium and potassium were not determined but the great concentration of these elements can be inferred from the other values. In the milk highest in sodium and potassium chloride, calcium and phosphorus concentration was extremely low. In one of these three cases (No. 29), the mother took unusually large amounts of table salt with her food. There was no report on this point with the other two.

Summary.

1. Analyses to determine the content of the various salts were made in thirty samples of woman's milk which appeared to have an unfavourable effect upon the infant or infants taking it : in seventeen samples in cases in which the infants were suffering from rickets and tetany and in thirteen in which there were other unfavourable symptoms supposedly due to the breast feeding.

2. The milks in the tetany and rickets group showed a tendency to be low in calcium and magnesium, high in sodium content. In the other group the tendency was to be high in total salt, sodium, potassium and chloride, though there were some markedly abnormal values found in respect to all the salts determined. Only two milks of this group showed no striking abnormality.

3. Whenever the blood calcium and phosphorus were determined and one or both were found to be lower than the normal, the calcium content of the milk was either lower than the normal limit or at least lower than the normal average.

4. The diets of all but one of the mothers represented in the tetany and rickets group were looked into and all were found to be more or less deficient in one or more of the following points :—total quantity of milk, sources of vitamines, especially the fat soluble, and total caloric value of intake. Three were deficient in all three respects.

5. In the group in which the infants showed unfavourable symptoms other than those of tetany and rickets, with two exceptions the milk analyses showed abnormal values for two or more salts, in many cases extremely abnormal values. Two of the mothers were accustomed to taking large amounts of table salt with their food.

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TABLE 1.

SALT CONTENT OF ABNORMAL MILKS: GRAMMES PER 100 C.CM. MILK.

Case No.	Name	Month	Total solids	Fat	Nitrogen	CaO	MgO	P_2O_5	Cl	Na_2O	K_2O	Na & K as chlorides	Total Ash
						GROUP A.							
1	Bak.	Mar.	13·17	—	—	·0363	·0056	·0464	·0392	·0145	·0801	·1545	·2343
2	Ro.	Mar.	11·54	2·5	·1551	·0349	·0102	·0618	·0346	·0365	·0324	·1203	·1830
3	Wa.	Apr.	10·68	3·75	·1185	·0317	·0041	·0375	·0350	·0156	·0537	·1148	·1719
4	He.	Jan.	11·49	2·7	·1979	·0295	·0056	·0431	·0429	·0467	·0705	·2000	·2635
5	Ca.	Mar.	11·51	4·4	—	·0367	·0067	·0541	·0379	·0161	·0723	·1450	·2076
6	Ha.	Mar.	9·90	1·5	·1261	·0331	·0070	·0357	·0494	·0281	·0538	·1384	·2067
7	Ste.	Mar.	12·94	—	—	·0384	·0064	—	—	·0355	·0719	·1811	·2711
8	Mar.	Feb.	12·72	3·5	·1694	·0276	—	·0584	·0290	·0166	·0979	·1866	·1483
9	Mi.	Jan.	11·70	3·4	·1379	·0285	·0029	·0291	·0340	·0100	·0861	·1556	·2340
10	Hun.	Jan.	11·26	2·0	·1876	·0378	·0022	·0345	·0246	·0086	·0665	·1217	·1914
11	Hut.	Feb.	12·32	2·65	·2184	·0395	·0075	·0284	·0411	·0260	·0732	·1653	·2489
12	Bi.	Mar.	13·51	4·3	·1876	·0431	·0040	·0352	·0330	·0308	·0572	·1489	·2125
13	Boe	June	12·36	—	—	·0290	·0074	·0258	·0475	·0284	·0618	·1517	·1928
14	Ch.	Feb.	10·43	—	—	·0290	·0035	·0418	·0309	·0195	·0584	·1295	·1823
15	Mat.	Feb.	13·0	3·9	·1838	·0384	·0069	·0466	·0394	·0192	·0644	·1384	·2124
16	So.	Dec.	11·92	—	—	·0498	·0076	·0337	·0449	·0068	·0254	·0532	·2410
17	DeR	Mar.	10·25	1·4	·1701	·0343	·0045	·0315	·0508	·0336	·0646	·1660	·2325
						GROUP B.							
18	Ja.	Feb.	13·59	—	—	·0150	·0009	·0625	·0462	·0138	·0658	·1304	·2347
19	Bo.	Feb.	10·39	1·3	·1743	·0540	·0064	·0264	·0469	·0227	·0533	·1275	·2258
20	Sta.	June	12·91	3·5	·1680	·0417	·0045	·0682	·0239	·0161	·0528	·1141	·1940
21	Au.	Nov.	12·90	3·5	·3024	·0633	·0076	·0625	·0697	·0355	·1079	·2383	·3477
22	Mas.	Sept.	11·56	—	·1736	·1003	·0117	·0540	—	—	—	—	·2250
23	I.W.	Feb.	12·85	—	·1799	·0345	·0057	—	—	—	—	—	·1719
24	Be.	May	9·77	1·1	·1477	·0463	·0051	·0741	·0674	·0283	·0607	·1498	·2463
25	Bar.	Mar.	13·57	3·9	·2342	·0412	·0148	·0414	·0554	·0357	·0622	·1662	·2504
26	Ho.	Nov.	9·92	1·2	·1667	·0356	·0038	·0243	·0546	·0436	·0559	·1711	·2273
27	Sc.	Nov.	13·30	3·7	·2583	·0356	·0002	·0437	·0413	·0316	·0841	·1931	·2547
28	Tu.	Oct.	12·75	3·2	·1774	·0409	·0040	·0316	·0317	·0060	·0925	·1582	·2270
29	Gi.	Jan.	8·95	0·9	·1834	·0412	—	·0161	·1488	—	—	—	·3881
30	Sm.	Oct.	7·46	2·2	·1995	·0095	·0055	·0142	·2566	—	—	—	·5607

TABLE 2.

RELATION TO NORMAL VALUES.

Case No.	Name	Age (mths)	Symptoms	Serum Ca. and P.	CaO	MgO	P_2O_5	Cl	Na_2O	K_2O	Total solids
1	Bak.	7	Tetany, and sl. Rickets.	Ca 9·7	—	—	+	ave.	ave.	++	+
2	Ro.	9	Tetany, and sl. Rickets.	Ca 5·6 P. 3·3	—	+	++	ave.	++++	— —	ave.
3	Wa.	8½	Tetany.		— —	— —	ave.	ave.	ave.	—	—
4	He	7	Tetany. Rickets.	Ca 5·0	— —	—	+	+	+++++	+	++
5	Ca.	12	Tetany. Rickets.	Ca 5·2 P 6·8	—	—	++	ave.	ave.	+	ave.
6	Ha.	7	Tetany. Rickets.	Ca 4·6 P 7·0	—	—	ave.	++	+++	—	ave.
7	Ste.	9½	Tetany. Rickets.	Ca 7·8 P 4·4	—	—	(n.e.)	(n.e.)	++++	+	++
8	Mar.	4	Tetany. Rickets.		— —	(n.e.)	++	—	ave.	+++	— —
9	Mi.	7½	Tetany. Rickets.	Ca 6·3 P 3·5	— —	— — —	—	ave.	—	++	+
10	Hun.	4	Tetany. Rickets.	Ca 6·2 P 6·4	—	— — —	ave.	— —	—	+	ave.
11	Hut.	2	Tetany. Rickets.		—	ave.	—	+	++	+	++
12	Bi.	3	Prem. Tet. Rickets.	Ca 7·6 P 3·0	ave.	— —	ave.	—	+++	ave.	ave.
13	Boe	6	Abscess. Rickets.	Ca 9·2 P 2·8	— —	ave.	—	++	+++	+	ave.
14	Ch. Twins	4	Anæmia. Rickets.	Ca 9·7—9·2 P 4·6—2·6	— —	— —	+	—	+	ave.	ave.
15	Mat.	8	Rickets.	Ca 6·8 P 2·0	—	—	+	ave.	+	+	ave.

n.e. = not estimated.

TABLE 2—*Continued.*

RELATION TO NORMAL VALUES.

Case No.	Name	Age (mths)	Symptoms	Serum Ca. and P.	CaO	MgO	P_2O_5	Cl	Na_2O	K_2O	Total Solids
16	So.	4	Rickets.		+	ave.	ave.	+	− −	− − −	+
17	DeR	5	Rickets.		−	− −	−	++	++++	+	+
18	Ja.	1½	Convulsions and vomiting ceasing on changed food.		− − − −	− − −	++	++	ave.	+	+
19	Bo.	7	Convulsions not tetany.	Ca normal	+	−	−	++	+	−	+
20	Sta.	2	Premature. Infants not thriving.		−	− −	+++	− −	ave.	−	ave.
21	Au.		Premature. Diarrhœa.		+++	ave.	++	+++	++ ++	++++	++++
22	Mas.	3½	Infant not thriving.		+++ ++	++	++	(n.e.)	(n.e.)	(n.e.)	+
23	I.W.		(Composite) Infants not thriving).		−	−	(n.e.)	(n.e.)	(n.e.)	(n.e.)	−
24	Be.	3	Inf. not thriving.	Ca normal	ave.	− −	++ ++	+++	+++	ave.	++
25	Bar.	3	Pyloric spasm. Slight eczema.		−	++++	+	++	++ ++	+	++
26	Ho.		Anæmia. Inf. not thriving.		−	− −	−	++	+++ ++	ave.	+
27	Sc.	½	Unaccounted for temperature.		−	− − − − − − − −	+	+	+++	++	++
28	Tu.		Vomiting ceasing on changed food.		−	− −	−	−	− −	+++	+
29	Gi.	4	Diarrhœa.		−	(n.e.)	− − −	+++ ++	(n.e.)	(n.e.)	+++ ++
30	Sm.	13	Infant not thriving.		− − − − − −	−	− − −	++++ ++++	(n.e.)	(n.e.)	++++ ++++

n.e.=not estimated.

THE PROTEIN AND NON-PROTEIN FRACTIONS OF SOME SAMPLES OF WOMAN'S MILK

BY

ANGELIA M. COURTNEY, B.A., and ALAN BROWN, M.B.

(From the Sub-Department of Pædiatrics, University of Toronto, and the Hospital for Sick Children, Toronto.)

A considerable number of large samples of woman's milk which was supposed to be the cause of the poor condition of the infants taking it have recently been analyzed at the Hospital for Sick Children to determine whether or not there was an abnormally high or low concentration of one or more of the salt constituents. The fat and total nitrogen content were also estimated in the samples when sufficient milk was available. The fat content was frequently found to be lower than normal but the nitrogen content, though tending to be slightly lower than average, never ran beyond normal limits. While this work was in progress the question arose whether the nitrogen distribution into the casein, lactalbumin and globulin, and non-protein nitrogen fractions might not in some cases show unusual values. Accordingly a series of determinations was made, not only in as many of the supposedly abnormal milks as possible but in a large number of samples of milk from wet nurses supplying the infant wards.

The nitrogen distribution commonly taken as normal is that ascribed to Schlossman as quoted by Rietschel[1] :—casein 41 per cent., lactalbumin and globulin 44 to 39 per cent., and residual nitrogen 15 to 20 per cent. Munk[2] is said to be the first to have called attention to the non-protein fraction, which is reported as about half in the form of urea and a large part of the remainder in amino-acids. The most complete contributions to the subject of the non-protein nitrogen fraction of woman's milk have been made by Frehn[3] and by Denis, Talbot and Minot[4]. There has been other valuable work on the subject by Macy et al.[5], Mader[6], Spirito[7], Giaume[8], besides a good many investigations into the difference between the acid and the rennet precipitation of the protein. Denis et al.[4] found a non-protein nitrogen content of ·020 to ·040 mgrm. per 100 c.cm. milk, which on the basis of an average total nitrogen content would be about 10 to 20 per cent. of total nitrogen. Frehn[3] reports 16·0 to 23·2 per cent. of total nitrogen as non-protein nitrogen. Macy et al.[5] give a value of 15 to 20 per cent. The values of Denis et al. seem to be a little lower than those of other investigators. They obtained the protein-free filtrate by precipitation first with copper sulphate, then a second precipitation in that filtrate

with calcium hydroxide and the removal of excess calcium as oxalate. This method was used in order to remove sugar and fat as well as protein, in preparation for applying their methods for estimating urea, amino-acids, etc. So far as could be ascertained the non-protein nitrogen fraction of the other investigators is the nitrogen content of the filtrate after precipitation in the milk with phosphotungstic acid. In the work here reported tannic acid was used as the protein precipitant, according to the procedure of L. L. Van Slyke[9]. It is claimed that cystin and the three basic amino-acids, lysin, arginin and histidin, are precipitated by phosphotungstic acid, as shown by D. D. Van Slyke in his scheme for the hydrolysis of proteins[10]. In a number of the milks analyzed in this study tannic acid and phosphotungstic acid were each employed as precipitant. In all these the nitrogen content of the tannic acid filtrate was greater than that of the phosphotungstic acid filtrate by 0·5 to 6·0 per cent. of total nitrogen, the average being about 2 per cent.

METHODS EMPLOYED.—The complete procedure in this study was as follows:—

20 c.cm. of milk was accurately measured into a 50 c.cm. volumetric flask and diluted with distilled water about 1 in 2, 2 c.cm. of 2 per cent. acetic acid were added slowly with shaking, and the stoppered flask was allowed to stand in the cold for twelve hours or more. After being made to volume, the contents were filtered through a dry high grade filter paper and samples were measured out for total nitrogen estimation according to the Kjeldahl-Gunning method. The remainder of the filtrate was gently boiled for 2 minutes, the lost water was restored and as large samples as possible were measured out for nitrogen estimation. Total nitrogen was also determined in 5 c.cm. samples of the original milk. When there was abundance of milk 40 c.cm. samples were measured into 100 c.cm. flasks for the first precipitation and acid added in proportion to the amount of milk used. With a few of the milks it was impossible to get a clear filtrate after the first precipitation. In such cases the values for the casein and the lactalbumin fractions have been omitted from the report. Usually the filtrate from the second precipitation was clear, sometimes faintly opalescent. It was assumed that the value found for total nitrogen, less that for the nitrogen in the first filtrate, gave the value for casein nitrogen, and the difference between the nitrogen values of the first and second filtrates gave the value for lactalbumin and globulin nitrogen. The filtrate obtained after boiling the acidified milk always contained more nitrogen than the tannic acid precipitate did. In 6 samples, in the filtrate obtained after boiling, a further precipitation was carried out with 50 per cent. sulphuric acid and saturation with zinc sulphate at 70°C. The filtrate obtained after this treatment contained distinctly less nitrogen than that present in the filtrate after boiling. The nitrogen removed by the sulphuric acid and zinc sulphate precipitation should represent a proteose fraction. Probably in some instances it included also nitrogen corresponding to part of the casein and lactalbumin fractions not completely removed by the first and second precipitations. The tannic acid precipitation was carried out by measuring 20 c.cm. of milk into a 100 c.cm. volumetric flask, diluting the milk about 1 in 3, adding approximately ½-grm. of sodium chloride and 12 per cent. tannic acid drop by drop until no more precipitate could be seen to form. After being allowed to stand for an half hour or longer, the contents were made to volume, filtered, and samples of the filtrate were measured out for nitrogen estimation[9]. The phosphotungstic acid separation was performed by adding to a measured amount of milk in a volumetric flask, for example, 20 c.cm. in a 50 c.cm. flask, one half the volume of 10 per cent phosphotungstic acid in 2 per cent. hydrochloric acid, allowing it to stand a short time, filtering and estimating nitrogen in filtrate.

This series of separations was carried out on thirty-six samples of milk of wet nurses, 1 to 5 samples from each of fourteen women and two composite samples. There was no definite reason to suspect these milks of being abnormal in any respect, since the infants taking them were doing as well as was to be expected. The same estimations were made in thirteen samples of milk

which appeared not to agree with the infants taking the milk. In four cases the infants were suffering from tetany and rickets, or rickets alone. With the others there were various unfavourable symptoms supposedly due to taking the mother's milk, such as convulsions not due to tetany, diarrhœa, failure to gain, and in one instance eczema.

When more than one sample of milk from the same woman was analyzed, the average of all the values found was used in the table. That the different samples from the same woman usually showed closely agreeing values at least suggests that the first and second precipitates usually represented pretty definite fractions of the nitrogen content.

The values found for the milks presumably normal are given in the upper half of the table, the other below. It is seen that very little distinction can be made between the values for the two groups. One only among the abnormal milks shows a divergence beyond the range of the values for the normal samples, that designated " Ka," in which the nitrogen content of both the tannic acid and phosphotungstic acid filtrates was much greater than that of any of the other samples. The infant taking this milk was suffering from eczema and improved on removal from the breast. Unfortunately fat and salt estimations were not made in this milk, so that other possible causes for the apparent harmful effect of the milk cannot be ruled out.

In most of the other milks not agreeing with the infants extreme abnormalities were found in the content of fat or of one or more of the salt constituents.

Thus it is seen that with one possible exception this entire series can be taken as showing a normal range of values for the casein, the combined lact-albumin and globulin, and the non-protein nitrogen fractions of the nitrogen content of mother's milk.

Though the investigation yielded negative results in the sense of not affording an explanation in certain cases in which mother's milk had an unfavourable effect, the results seem to be worth reporting if only for the purpose of again calling the attention of pædiatrists to the large proportion of the nitrogen of woman's milk which is not in the form of protein, and which, according to Munk and to Denis *et al.*, is about 50 per cent. in the form of urea.

This proportion is far greater than that of the same fraction of cow's milk, though the actual quantity, mgrm. per 100 c.cm. is about the same in both, according to results obtained in this laboratory as well as those reported by Denis and Minot[11]. We found for the average in thirteen samples of cows' milk (herd milk) 7·2 per cent. of total nitrogen in the tannic acid filtrate and 5·4 per cent. in the phosphotungstic acid filtrate. As cows' milk contains from two to three times, usually nearer three times, as much nitrogen as woman's milk, it can be seen that the actual amount present must be nearly the same in both kinds of milk.

Another point brought out by this study is the difference between the nitrogen content of the filtrate after precipitation in the milk by tannic acid and the content after precipitation by phosphotungstic acid, this difference being presumably a measure of the content of cystin and the basic amino-acids, lysin, arginin and histidin. The thirteen samples in which this was

estimated showed a variation, as above stated, of from 0·5 to 6·3 per cent. of total nitrogen, the extremes being found in samples which were normal as judged by the condition of the infants taking the milk. Whether this varying content could have any significance in connection with the well-being of the infant is a question which would require a much more extended investigation than this to determine. That such an investigation might be worth undertaking is suggested by the importance for growth of some of these amino-acids.

Summary.

1. A partial nitrogen partition was carried out on a series of samples of woman's milk, part of them supposedly normal and part supposedly abnormal in some respect. With one possible exception the nitrogen partition showed no distinctions between the two groups. The total nitrogen content ran slightly lower than the usually accepted average. The casein fraction of total nitrogen ranged from 9·7 to 49·2 per cent. of total nitrogen (average 31·8 per cent.), and the lactalbumin and globulin fraction from 19·0 to 57·7 per cent. (average 31·6 per cent.). Total non-protein nitrogen, that remaining after precipitation of protein by tannic acid, ranged from 11·0 to 27·5 per cent., with one possibly abnormal value of 42·0 per cent. (average 21·9 per cent. of total nitrogen). The non-protein nitrogen remaining after precipitation with phosphotungstic acid ranged from 11·2 to 22·3 per cent. of total nitrogen, with 36·4 per cent. in the possibly abnormal sample (average 19·8 per cent.). The difference between the last two averages, 2·1 per cent. of total nitrogen, represents the content of cystin and the basic amino-acids, lysin, arginin and histidin.

2. The large proportion of the nitrogen content of woman's milk in the form of non-protein nitrogen is emphasized.

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TABLE

	Total N. grm. per 100 c.cm.	Per cent. of total nitrogen as :—				
		Casein N.	Lactalb. and glob. N.	*Total non-prot. N. (including proteose)	N. of tannic ac. filtrate	N. of phospho-tungstic ac. filtrate
Bo. wetnurse—ave of 3	·2436	28·8	38·7	32·5	21·1	16·6
D. „ „ 3	·2303	9·8	44·4	45·8	22·0	19·3
Ha. „ „ 5	·2081	33·0	31·7	35·3	22·6	19·7
Composite of wetnurses' milk	·2002	41·2	30·8	28·0	19·0	18·5
Gr. wetnurse—ave. of 3	·1923	43·6	25·3	31·1	24·9	21·0
An. wetnurse ...	·1855	40·1	28·3	31·6	21·2	—
Composite of wetnurses' milk	·1778	38·0	30·6	31·4	21·6	—
Sn. wetnurse	·1757	—	—	27·9	—	11·2
R. „	·1722	45·8	19·0	35·2	20·3	17·5
J. wetnurse—ave of 3...	·1706	34·5	31·6	33·9	22·1	—
Bu. „ „ 2...	·1687	22·3	33·6	44·1	13·5	—
Q. „ „ 3...	·1682	26·7	31·9	41·4	27·5	21·2
V. „ „ 3...	·1652	49·2	23·3	27·5	20·3	—
F. „ ...	·1435	35·6	25·4	39·0	24·9	19·7
Sl. „ „ 2...	·1421	31·2	25·5	43·3	25·1	—
Be. „ „ 3...	·1374	34·7	30·2	35·1	21·8	—
Average for normal women	·1801	34·3	30·0	35·2	21·9	18·3
Au. Premature inf., early milk, inf. diarrhœa	·3024	13·8	57·7	28·5	14·8	—
Sc. Two weeks' old inf. with unaccounted for temp. ...	·2583	36·3	31·2	32·5	—*	—
J. Six weeks' old inf., convulsions & vomiting ceasing on change of food ...	·2275	—	—	39·4	20·1	18·8
Hu. Two months' old inf., tetany and rickets	·2184	27·4	38·6	34·0	—	—
Sm. 13 months' old inf., infant not thriving	·1995	17·4	46·0	36·6	11·0	—
K. Early milk, inf. with eczema, not gaining, improved on change of food	·1932	9·7	34·3	56·0	42·0	36·4
Bi. 3 months' old inf., premature, tetany and rickets ...	·1876	29·1	32·2	38·7	26·1	—
Gi. 4 months' old inf., diarrhœa	·1834	—	—	25·8	—	—

TABLE—*continued.*

	Total N. grm. per 100 c.cm.	Per cent. of total nitrogen as !—				
		Casein N.	Lactalb. and glob. N.	*Total non-prot. N. (including proteose)	N. of tannic ac. filtrate	N. of phospho-tungstic ac. filtrate
Boy. 7 months' old inf., convulsions not tetany	·1743	44·8	21·6	33·6	—	—
Ma. 3½ months' old inf., not thriving ...	·1736	37·5	26·7	35·8	—	22·3
DeR. 5 months' old inf., rickets	·1701	35·7	28·3	36·0	23·0	—
St. Approx. 3 months' old inf., prem. Infant not thriving	·1607	31·2	31·4	37·4	17·1	15·2
Mi. 7½ months' old inf., tetany and rickets	·1379	30·2	22·2	47·6	—	—
Average of abnormal milks	·1982	28·5	33·7	37·1		
Average of all ...	·1886	31·8	31·6	36·0	21·9	19·8

*This may also include some nitrogen belonging to protein not brought down in the precipitations.

TREATMENT OF CHOREA BY NIRVANOL

BY

HUGH T. ASHBY, M.D., F.R.C.P.

(From the Royal Manchester Children's Hospital, Pendlebury.)

I am indebted to Poynton and Schlesinger[1] for the suggestion that nirvanol should be given a trial in the treatment of chorea. Twelve well marked cases have been treated with this drug alone, and the results are encouraging in that all the cases have done well and the course of the disease has been shortened.

All the cases were in hospital and under close supervision in bed the whole time. No unfavourable symptoms developed, except in one child, who reacted rather severely. This was a particularly nervy child with very marked chorea. She did remarkably well in the end.

Nirvanol is a white powder, tasteless and readily taken by children. One dose each day is given, generally in the evening. The dose administered was $3\frac{1}{2}$ grn. to children up to the age of 10 years and 4 grn. to older ones.

After about 8 daily doses a rash appears and the drug is stopped at once and no treatment other than rest in bed is undertaken.

Eight days seems to be the average for the rash to appear. In one case in which the rash was particularly well marked it appeared on the fifth day. The rash was not accompanied by any rise of temperature, except in the case mentioned, when it came on the fifth day.

Some of the children, especially the girls, were noticed to be incontinent of urine the evening before the rash appeared, and the onset of the rash could be forecast by this phenomenon. The incontinence lasted for a few hours only and had disappeared by the next morning.

The rash nearly always started on the back of the hands or on the buttocks, and then spread to the trunk. Pressure points such as the elbows and buttocks were specially affected. There was practically no rash on the face. The rash is visible for about four days. It is faintly visible for one day, is well marked for two days, and takes one day to fade and completely disappear. It is essentially toxic in appearance and varies in intensity on the different parts of the body within a short time. While painting the rash for me, Miss Davidson noticed this characteristic and corroborated the fact on her own observation.

The rash is very slightly raised and can just be felt. It is morbilliform and like measles except that the papules are liable to become more confluent. In fact anyone seeing a nirvanol rash would at once say that the case was one of measles.

Nivuanol Rash.

The children were not inconvenienced in any way by the rash, the pulse rate was hardly increased and there was no irritation. In a few cases there was a slight conjunctivitis during the period of the rash, but no other complications were noticed. The urine was always free from albumen.

An interesting point was that some of the children lost the knee jerks at about the time the rash appeared, and they did not return for a few days. The choreiform movements were slightly aggravated at this time, but they quickly settled down and disappeared.

The heart lesions, present in a few cases, were not adversely affected: in fact rather the opposite was found.

Like Poynton and Schlesinger's cases, there was a marked increase in the eosinophils of the blood at the rash period. A week later the blood became normal.

Conclusions.

The treatment of chorea by nirvanol appears to be safe as long as the child is kept under close observation and the dose does not exceed 4 grn. a day.

The general course of the disease is shortened and improvement is more speedy than with other methods usually adopted. At the end of the third week the children were steady and ready to leave hospital, and there have been no relapses so far.

A point in favour of nirvanol is that the chorea may be checked before the rheumatic infection does harm to the heart.

Severe secondary reactions have been reported after exposure to artificial sunlight just after children had finished a course of nirvanol, and this latter should not be given until some weeks have elapsed.

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THE NIRVANOL TREATMENT OF CHOREA

BY

WALTER M. WHITAKER, M.D.

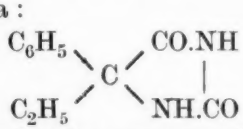
House Physician, East London Hospital for Children.*

Various methods and drugs have been used in the treatment of chorea minor in children; among them are sodium salicylate, liquor arsenicalis, arsphenamine, bromides, milk injections, magnesium sulphate, thyroid extract, luminal, chloretone, and adrenalin subcarbonate. Medical literature reveals a percentage of good results from each of them, but since chorea is a more or less self-limited disease, a certain amount of scepticism accompanies any claim of cure.

One of the more recent and judging from the favourable foreign reports, most successful modes of therapy is nirvanol, a hypnotic which was first introduced for the treatment of chorea by Freda Roeder[1] in 1919. Poynton and Schlesinger[2] reported favourable results in six cases during 1929. Apparently these are the first to be reported in English literature, though Cunningham[3] at the Strong Memorial Hospital at Rochester, New York, treated about a dozen cases of chorea in 1928 with favourable results. These, to date he has not published.

During the past few months (April to September 1929) it has been the writer's good fortune to treat eleven cases of chorea with nirvanol. These were in the wards of the East London Hospital for Children under the care of Drs. Geoffrey Bourne, Batten, Simpson, and Chodak Gregory, to whom I am indebted for permission to publish them. The favourable results in these cases, and the sparse English literature on the subject, are the reasons for their publication. It is also hoped that others will be stimulated to investigate further this mode of therapy.

Nirvanol is a white tasteless powder which is chemically phenylethylhydantoin having the formula:



Luminal is closely allied to this but has one more CO group. Nirvanol belongs to the barbituric acid group, and not only has their usual hypnotic action but also seems to possess the power of producing a febrile reaction and an exanthem more often than any other known drug of the kind when given over continued periods. To this exanthem and enanthem de Rudder[4] has given the name 'nirvanol sickness' The intensity and completeness of nirvanol sickness varies in different cases. The curative effect in chorea is apparently due to the bodily reaction produced by the sickness.

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* Under the Reciprocity Scheme with Barnes Hospital, St. Louis, U.S.A.

The production of nirvanol sickness.

To produce nirvanol sickness, the drug is given orally in a dosage of 0·3 grm. per day to children of 3—14 years of age until the appearance of an exanthem or enanthem, or both. This interval of time in most cases is from 7 to 14 days after the onset of administration. Usually the exanthem takes the form of a morbilliform rash which is often accompanied by pyrexia. Before the onset of the fever and rash, in many cases drowsiness is noted for 2—4 days. In the eleven cases here reported, so often was this present that it was possible to predict the imminence of the reaction by the degree of drowsiness present three or four days after beginning the drug. With the onset of any signs of nirvanol sickness, the drug is discontinued. Rest in bed is ordered during the administration.

Recognition of the rash may entail a close search. Usually it appears first on the torso and elbows; then in a few hours it has become generalized, probably involving the palms of the hands and the soles of the feet. It is most often of a morbilliform character, remains discrete, but sometimes becomes confluent on the elbows or knees. Of the reported cases all but one were of the morbilliform type, though urticarial and scarlatiniform varieties are known. Case 2 showed a discrete, blotchy, urticarial rash on one arm only. In general the face seems to escape the eruption but often shows a marked erythema and circumoral pallor. Case 11 approached a scarlet type. Desquamation was noted in those cases showing a severe reaction. Accompanying the rash in most cases is a raised temperature (103—104°) and a rise of pulse rate to perhaps 140 for three or four days. Usually the rash and fever subside simultaneously. There is often a complaint of headache, burning eyes, occasional diplopia, mild sore throat, and œdema of the face has been seen. No œdema was noted in the present series but headache and conjunctivitis were common. There was no vomiting, but this symptom may occur. Cases may remain afebrile throughout the course and yet develop a marked rash; as occurred in Cases 5 and 10; or may show no rash but have a fever as in Case 6; or may show neither a rash nor fever as occurred in Cases 4 and 9. But in general the pyrexia seems proportional to the severity of the rash.

Some observers have considered it useless to administer the drug longer than for a period of 14 days (de Rudder[4], Huber[5]), but in two of the Shadwell cases no symptoms of nirvanol sickness were noted till the fifteenth day in Case 6, and the seventeenth day in Case 5. The standard dosage of 0·3 grm. per day had been given. In Case 4 the drug was given continuously for twenty-two days before signs of nirvanol sickness appeared and at this time the child complained of diplopia. It would seem from the present series that those cases which react within 7—12 days show the most marked symptoms of the sickness and this opinion is held by Lichentritt, Lengsfeld, and Silberberg[6]. Lesigang[7] reports one case in a hundred that reacted with exanthem to a single dose.

Following the cessation of the sickness, or during it, there is noted a diminution in the movements. This may be almost dramatic in its suddenness, but in the Shadwell cases the improvement tended to occur within the

first week or ten days, and there was in some cases complete loss of chorea within such a time. Many of these patients lose their gross bodily movement but retain the finer movements (e.g., tremor of hands) for several weeks after the reaction. If chorea is the result of an organic cerebral lesion this is not surprising, for no drug can be expected to remove rapidly both the cause of a disease and the gross local structural damage. Secondary reactions have occurred several days after the sickness with a return of the rash and fever. Keller[8] has suggested that these may have been due to exposure to the sun. Two of our patients were exposed to direct sunlight for three or four hours daily for five days during the first week after their reaction, and neither of them showed any signs of relapse.

Cases apparently resistant to nirvanol are met, in which neither rash nor fever occurs. There were two such cases in this series. In them, examination of the blood is very important, since Poynton and Schlesinger[2] suggest that eosinophilia may at times be the only evidence of nirvanol sickness. De Rudder tried to induce serum sickness in two of his cases that were resistant to nirvanol, by giving repeated doses of serum over a period of several days but both failed to show any signs of serum sickness, so he suggested that such cases were immune to anaphylaxis. Such a statement seems illogical.

In the two Shadwell cases which failed to exhibit an exanthem and enanthem, the administration of 10—20 million of killed B. typhosus intravenously, resulted in a reaction consisting of a temperature and pulse rise 6—12 hours later. So these patients do not seem immune to protein shock.

Among the changes in the blood in nirvanol sickness the most common finding is that of an eosinophilia about the height of the reaction. Within two weeks in all cases the eosinophil count had returned to about the same percentage as had been found on admission. Several observers have stressed the presence of an eosinophilia in chorea. Cabot[9] found the blood normal in chorea except for increased eosinophils in twelve cases. Berger[10] reported forty cases with a general average of 7·6 per cent. and found no relation between the severity of the chorea and the percentage of eosinophils. In the cases here reported six out of ten cases showed an eosinophilia on admission, considering 2 per cent., or about 120—140 eosinophils per c.mm., as the upper limit of normal. With nirvanol eight out of eleven cases showed a definite further increase, the total eosinophil figures in all the cases seriatim at the height of the reaction were, 350, 0, 750, 300, 520, 140, 780, 1,050, 550, 2,330, 90, 260 and 1,060 per c.mm. If there was no obvious reaction as evidenced by absence of fever or rash, then the blood was ex nined when the drug was suspended. In Cases 4 and 9 in which no exanthem or enanthem appeared, there was at the end of 22 and 17 days of administration respectively, an eosinophilia of 280 and 550 per c.mm. These children did definitely improve and one is ead to believe that the eosinophilia was the only sign of a reaction. This confirms Poynton's and Schlesinger's suggestion as to the importance of watching the blood picture. These two cases also showed a relative lymphocytosis on the cessation of the drug with a decrease in the polymorphonuclears, a change

also described elsewhere as occurring during the reaction ; but there were only three cases out of eleven in which there was found a relative lymphocytosis at the time of reaction. From this series therefore not much stress could be placed upon the constancy of a relative lymphocytosis, although it may perhaps be of value in ascertaining whether or not a reaction has occurred.

In ten cases at the height of the reaction, the polymorphonuclear cells were increased above the admission figures in four cases, decreased in three cases, and virtually the same in three cases.

During the administration of the drug the desirability of watching for a leucopenia has also been stressed ; but the lowest leucocyte count recorded in our series was 4,800. Six out of ten cases at the height of the reaction showed a figure slightly reduced from that of admission, three were unchanged and only one (Case 2) showed a figure definitely higher than that of admission. This may be explained in Case 2 by the presence of a recent tonsillar infection a few days before starting to administer the drug, which may have served to elevate the count (the admission count was done two weeks before the drug was started).

Cases 3, 8, and 10 which showed the most marked eosinophilia did not seem to make a more rapid recovery than the other cases, in fact, the most speedy recovery occurred in Case 11 which showed only 88 eosinophils per c.mm. at the reaction time. From these few observations it seems that the degree of eosinophilia is of little value in prognosis as to the rate of recovery, but that eosinophilia itself is a very common sign of the sickness. Those cases showing a definite general reaction as evidenced by rash and fever with or without an eosinophilia seemed to improve the most rapidly, but Cases 4 and 9 did definitely improve without.

In no case were there any urinary findings of an abnormal nature during the course of nirvanol administration or subsequently.

Examination of the red blood cells and hæmoglobin on two cases two weeks after the reaction showed no alteration. No changes were noted in the cardiac status during the treatment of those three cases (1, 2, and 3) showing cardiac lesions.

Cases 12 and 13 were two convalescent children in whom nirvanol was tried, merely as controls. They developed the usual effects. Case 12, a case of catarrhal jaundice, developed a typical rash with fever and increase in pulse rate, after eight days of administration, which lasted for five days with an eosinophilia of 260 per c.mm. Case 13 was convalescent from lobar pneumonia, and was completely recovered when given nirvanol. A reaction occurred on the eighth day with a typical nirvanol rash and fever, and an eosinophilia of 1,060 per c.mm. In both cases there were no obvious differences from the reaction which occurs in chorea cases.

Action of nirvanol.

Some interesting ideas have been advanced as to the manner in which nirvanol is able to produce its bodily effects. Biologically, de Rudder[4] considered the reaction produced by the drug as being closely allied to serum sick-

ness and that the success of the drug lay in the fact that during its administration a blood alkalosis was induced with a sudden shift to acidosis at the time of the reaction, the abrupt change having an effect on the central nervous system. Poynton and Schlesinger[2] in two of their six cases studied the blood-plasma bicarbonate and noted an increase in the plasma bicarbonate in both cases during administration of the drug, but could demonstrate no tendency to acidosis at any stage of the treatment.

Using the colorimetric method for determining blood pH as devised by Dr. H. A. Ellis of London, on five of the present series at the height of their reaction, the pH was very constant, ranging from 7·25 to 7·4, with three cases at 7·3. Since this is a colorimetric method it is of course liable to the error involved in such readings, but the normal range of the figures merely bears out the recognized constancy of the pH of the blood except in the terminal stages of disease. However, such figures are not conclusive that an acidæmia may not have existed, but it was apparently not of a sufficient degree to affect the pH noticeably.

Since nirvanol is primarily a hypnotic and acts essentially as a depressant to the central nervous system, it might be argued that the fever was of central origin; but Lesigang[7] was able to show that antipyrin was without effect in shortening the duration of fever in two cases of nirvanol sickness. This tends to rule out the possibility of direct stimulation of the heat regulation mechanism by nirvanol. As the drug is primarily a depressant it is unlikely to stimulate the centre. Moreover the hypothesis takes no account of the constant latent period which precedes the fever. The pyrexia is not entirely dependent upon the presence of the exanthem for cases occur with rash and no fever whatever, and vice versa.

Nirvanol seems to act cumulatively, as was shown in the cases here reported by the increased drowsiness after a few days of administration. The two cases which did not react with a rash exhibited this effect, which may well be due to the hypnotic action of the drug. Lesigang[7], who used nirvanol in 106 cases of chorea, pertussis, epiplepsy, and other conditions, noted the tendency to drowsiness in most of his cases.

The symptom-complex present in nirvanol sickness may be met in the administration of other drugs which produce rashes, but is more frequently elicited by nirvanol than by other drugs. The rare instances of exanthem production after one or two doses (such as may occur in one in fifty or a hundred cases) are likened to drug idiosyncrasy by Lesigang[7]. In these cases a rash results after the first known contact with the foreign substance, but true nirvanol sickness comes only after a rather set period of administration, that is, a series of contacts with the drug. So although the symptoms are comparable with idiosyncrasy, the mode of production is different.

Lesigang[7] was able to induce fever and rash in eleven out of twelve cases, which had previously had typical nirvanol sickness 18—39 days before, by the exhibition of one dose of nirvanol (0·3 grm.). In one child a reaction was induced six months after the initial sickness by one dose and again five months later, a total of eleven months after the original sickness. In three of our

cases (8, 10, 11), which alone were so tested, it was possible to induce fever, rash, and a pulse rise about 6—10 hours after a single dose of 0·3 grm. of nirvanol. The reaction evoked in such cases was of a very mild character as compared with the original sickness. Since the vast majority of cases do not react to a single dose of the drug and since the appearance of the reaction occurs in a fairly fixed manner after repeated doses, apparently the conclusion to be drawn is that the body-tissues have become altered by the previous doses, so that instead of the simple narcotic action which normally might result from one dose, a modified effect occurs, in reality an active sensitization of the body to nirvanol. The occurrence of such a reaction from one dose of the drug given several weeks after the initial nirvanol sickness, can hardly be due to any cumulative effect, since Lesigang[7] mentions that a child given 0·5 grains of luminal three times per day for thirty-four days, showed evidence of the drug in the urine for only eight days after ceasing administration, and being so closely allied to luminal, nirvanol is probably excreted at a similar rate. It would thus seem that the organism reacts as to a narcotic cumulatively for a certain period, usually 7—12 days of dosage, and that it is then actively sensitized to the drug, nirvanol sickness developing, so that the administration of a single dose several weeks after, will in most cases again induce signs of reaction.

That the rash and fever are more pronounced after 7—12 days, than the same reaction induced by a single dose several weeks later, probably depends solely on the greater available quantity of nirvanol present when the initial reaction is induced. This seems borne out in Case 1 in which the drug was not discontinued promptly on the appearance of symptoms but was given for three or four days after the rash appeared in 2·5 grain doses : the total febrile period was one of 9—10 days which was a much more severe reaction than when the drug is discontinued promptly.

Lesigang[7] thinks that nirvanol sickness is an allergic phenomenon rather than anaphylaxis as is maintained by de Rudder[4]. Lesigang bases his ideas on the criteria that anaphylaxis implies : (1) that the substance acting should be a protein antigen, (2) that passive transmissibility must exist, and (3) that acquired specific sensitivity is possible. He was unable to fulfill the second requirement when he had occasion to give a transfusion in which he took the blood from a child with nirvanol sickness and gave it to a two year old child, to whom he gave nirvanol in small doses but was unable to elicit a reaction. From its chemical formula, nirvanol is seen to be a non-protein antigen and according to Doerr[11], anaphylactic phenomena can only be produced by protein antigens. So nirvanol sickness seems not to be due entirely to an accumulative effect, neither is it caused by idiosyncrasy or anaphylaxis; but it comes in that group of reactions known as allergic phenomena and which occur as intermediate gradations between the poles of idiosyncrasy and anaphylaxis (Doerr[11]).

The exact mechanism of the good effects produced in chorea still seems to be a puzzle. Cases appear to improve whether the marked signs of sickness, such as fever and rash, are or are not produced. Moreover, the eosinophilia c

seems to be only a frequent accompanying factor. The hypnotic property must not be forgotten. Those cases having the most severe reaction do certainly seem to show the most marked and rapid improvement. Apparently then such a 'shake-up' of the body metabolism does in some way, as yet unknown, alter the condition of the central nervous system and thereby produce an improvement in the chorea. There seems to be no evidence in the English literature to support the idea that a sudden shift in the acid-base balance of the blood is induced at the time of the reaction.

Further biochemical investigations and careful clinical observations are desired to ascertain how the beneficial effects are induced.

Hints on therapy.

It is obvious that the use of a drug like nirvanol which is sometimes capable of producing alarming symptoms should only be undertaken in a hospital or in carefully controlled practice, but in this series no alarming symptoms were noted at any time. Leucopenia seems rare but the blood should be watched for evidence of a falling leucocyte count, or eosinophilia, since the latter seems sometimes to be the only sign of a reaction. The drug should be given dailyin doses of 0·3 grm. till a reaction or signs of toxicity occur and then omitted. To a child 13—14 years old, 0·6 grm. may be given. Treatment seems worth continuing for 15—20 days before stopping. An approaching reaction may be guessed by the presence of drowsiness after 3 or 4 days of the drug. The child should be kept at strict rest in bed during the treatment.

Before nirvanol was used in 1919 for chorea, it had been used as a hypnotic in adults in whom it often reacts more quickly and more sharply, though a rash was more rarely seen[7].

Majerus[12] described a fatal case of acute hemorrhagic nephritis associated with a severe bullous exanthem which he attributed to nirvanol, but it must be noted that this patient had a streptococcal empyema of four weeks duration. Hæmaturia has been reported. Matzdorff[13] recorded a case of toxicity without an unduly high dosage in which the child became comatose without an exanthem, but recovered shortly.

Such instances serve to demonstrate the potency of the drug, and to point to the necessity of careful observation during therapeusis, but certainly in the vast majority of cases the unpleasant signs and symptoms are insufficient to cause much distress either to the patient or the clinician. The good results of the cases treated in Germany by Huber[5] (20 cases—18 definitely improved), Lesigang[7] (31 cases,most of which were definitely improved), Keller[8] (nine cases), and the cases of Matzdorff[13], F. Roeder[1], Rietschel, and others are all evidence of the success and extent to which this drug is being used in Germany.

Conclusions.

The nirvanol treatment has been tried in eleven cases of chorea minor and in two control cases. Signs of nirvanol sickness were induced in nine of the eleven cases, and if eosinophilia may be considered as sufficient evidence

of a reaction when occurring alone, then all cases may be said to have reacted. Marked reactions occurred in two non-choreic children simulating those seen in chorea cases in all respects. The majority of the observed cases showed a marked lessening up to complete absence of active chorea within the first week after the reaction, and in all there was no active chorea one month later. Improvement appears to be greatest in the violent and paralytic cases, mild cases, with continuous slight movements, being less benefited. Post-choreic tic, with repetition of one or more definite movements may occur in spite of the treatment. No relapses were seen.

Nirvanol certainly seems worthy of a trial especially in the more severe cases of chorea. Its effect on the ultimate prognosis remains to be seen.

I am greatly indebted to Dr. Temple Grey of this Hospital for the translation of the German literature.

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Case	Age and sex	Duration of chorea	Previous treatment	Severity	Dosage of nirvanol
1	8 years, fem.	8 months at intervals.	Given arsenic and soda sal. in O.P.D.	Three plus.	35 grain in 7 days. Also 7 grains after first signs of reaction. Total 42 grains
2	7 years, fem.	Attacks for 2 yrs. Duration of present attack 5 months.	Bromides and salicylates.	Four plus.	35 grains in 7 days.
3	12 years, male	Attacks since 1926. Duration of present attack 5 wks.	Sal. and bromides for 5 wk.	Two plus.	45 grains in 9 days.
4	8 years, fem.	Previous attack 8 mo. prior. Present attack of 3 wks. duration.	Sal. and arsenic and bromides for 3 wk.	Three plus.	75 gr. in 15 days; 53 gr. in 7 days. Total of 128 gr. in 22 days.
5	7½ years, fem.	Previous attack 7 mo. prior lasting 6 mo. Present attack 3 mo.	Sal. and arsenic for 1 mo.	One plus.	55 gr. in 11 days; 45 gr. in 6 days. Total 90 gr. in 17 days.
6	12 years, fem.	Chorea since 1927. Under care of several hospitals.	Sal., arsenic, bromides. Bed rest. Hospitals.	Four plus.	75 gr. in 15 days.

Symptoms of "sickness"	Height and duration of fever	Progress	Remarks and results
Quieter after 5 days. Drowsy. Temp. 103, Pulse 120 on the 7th day. Rash 8th day. Lacrymation. Maculo-erythematous rash lasting 5—6 days.	103–104 for 6 days. Normal in 10 days.	Less chorea at time of reaction. 2 wk. after the reaction, no active chorea. In hospital for 6 wk. (4 wks. after reaction).	Desquamated 1 mo. after reaction. Heart lesion unaffected. Gaining weight. No active chorea 3 months after. Fine tremor of hand persists.
T.P.R. rise on 7th day. Blotchy discrete erythema on right arm and face.	Temp. for 4 days. To 103·5 on first day.	Tonsillitis 10 days prior to drug. Drowsy 1 day. Less choreic 2 days after reaction. 3 wk. after reaction had temp. to 100 and blotchy rash of face and torso for few days associated with a follicular tonsillitis. In Hosp. 15 weeks. Polys 71%, Lym. 23%, Eosin 3·5%, Monos. 2·5%.	Tonsillectomy 5 wk. after the reaction. Progressive improvement in chorea, also in mental stability. No movements 1 mo. after reaction.
After 9 days had a rash on torso. No temp. or pulse rise till 10th day. Generalized morbilliform rash, lasting one day, followed by erythema lasting 3 days.	To 100 F. for 4 days.	Drowsy 3-4 days prior to reaction. Less chorea in 3rd wk. Heart as before. Loss of movements was gradual. Marked improvement in mentality and general appearance. In hospital a total of 6 wk.	Chorea gone when observed 1 mo. after discharge from hospital. Slight œdema of ankles. Sent to Bognor. No relapse.
None, but diplopia and burning of eyes after 22 days. No rash.	None.	Drowsy after 10–12 days. Definitely less choreic after 3 wks. of the drug. No chorea when discharged. In hospital 7 wk. (4 wk. after the cessation of drug).	Given 20 million killed B. Typhosus intravenously, 2 wk. after suspension of drug. Prompt fever and pulse rise. No relapse.
Slight rash. No fever Pulse to 110 on first day. Rash morbilliform. Only on forearms. Erythema of face.	None.	Drowsy during the drug's adm. Movements less first wk. after reaction. In hospital 7 wk. (4½ wk. after reaction).	Movements gone 1 mo. after reaction.
No rash. Fever and pulse rise after 15 days.	100 F. for two days.	Movements sl. less prior to reaction. Much less 3—4 days after reaction. No active chorea 1 mo. later. In hospital 13 wk. (10 wk. after reaction) Up for 5 wk. before discharge.	Considering the severity of this case, improvement was rapid and excellent. The good effects were noted within a few days after the reaction.

TABLE *contd.*

SYNOPSIS OF NIRVANOL-

Case	Age and sex	Duration of chorea	Previous treatment	Severity	Dosage of Nirvanol
7	10 years, male	5 wk.	Bed rest at home for 4 wks. with no improvement.	Two plus. Speech affected.	35 gr. in 7 days. 22 gr. in 3 days. Total 57 gr. in 10 days.
8	13½ years, male	Chorea for 3 mo. in past year. Present attack of 2—3 mo. duration.	Negligible.	Two plus.	55 gr. in 11 days.
9	6 years, fem.	9 months.	Negligible.	Three plus.	60 gr. in 12 days. 37 gr. in 5 of 97 gr. in days. Total 17 days.
10	5 years, fem.	1 wk.	None.	Three plus.	45 gr. in 9 days.
11	9 years, male	Had had 3 attacks in past 2 yrs. Present one of 4 wk. duration.	None.	Four plus.	40 gr. in 8 days.
12	5 years, male	Convalescent catarrhal jaundice used as a control.			40 gr. in 8 days.
13	4 years, male	Convalescent lobar pneumonia used as a control.			40 gr. in 8 days.

Severity of Chorea.

One plus (+).—Mild movements. No speech defects. Able to feed self.

Two plus (++).—Moderate degree of movements. Able to feed self.

Three plus (+++).—Very marked movements. Emotional. Speech defects. Unable to feed self

Four plus (++++) —Bodily injuries from movements. Unable to feed self. Mental instabilities. Speech defects

TREATED CASES.

Symptoms of "sickness"	Height and duration of fever	Progress	Remarks and results
Morbilliform rash on hands, and fever on 10th day. Rash was general on 11th day. Pulse 110. Lacrymation. Headache.	Fever for 4 days. Peak 102 F.	Drowsy 2—3 days before reaction. Definitely less choreic and speech unaffected, the first wk. after reaction. In hospital 7 wk. (5 wk. after reaction).	No active chorea 10 days after reaction. Speech normal. Gaining weight Very slight fine tremor of hands persists.
Fever. General morbilliform rash, headache, pulse rise. Conjunctivitis.	Fever of 102·5 for 4 days. 100 for 1 day.	Drowsy 2—3 days prior to reaction. Definitely less choreic first wk. thereafter. No active chorea 10 days later. No chorea one mo. later. In hospital for 7 wks. (5 wk. after reaction).	In sunlight for few hours for 5 days without relapse. Tonsillectomy 2 wks. after reaction. nirvanol gr. V, 3 wk. after reaction. Developed slight rash on forearms 10 hrs. later. No chorea on discharge. Nirvanol gr. 7½ gave a temp. to 99 F. and a pulse of 100 when given 4 wks. after the initial reaction.
None. No rash.	None.	More quiet after 2—3 days of drug. Movements less during adm. of drug and no active chorea 1 wk. after drug was cessated. In hospital 7 weeks.	Definitely improved. Given I.V. Typhoid one wk. after drug was discontinued (10 million). Reaction with temp. and pulse rise a few hours later.
Generalized morbilliform marked rash. Most marked on elbows and knees. No fever or pulse rise, till two days after rash appeared.	None.	Drowsy 2 days prior to reaction. Movements less two days after rash subsided. Steadily improving. In hospital 5 wk. Chorea developed during child's convalescence from pneumonia in the hospital.	Has definitely improved but not so rapidly as most of the other cases. Given 5 gr. of nirvanol 2 wk. after her reaction. Drowsy 2—3 hr. later. Rash and pulse rise 10 hrs. later. No fever. Signs had disappeared in 18—24 hours.
Temp. and pulse up followed by a generalized morbilliform rash on 9th day. Was giddy. Conjunctivitis.	102–103 for 6 days.	Drowsy 2—3 days prior to reaction. Definitely less chorea during reaction. No chorea 1 wk. after reaction. Still in hospital.	Almost a dramatic recovery. Given 5 gr. of Nirvanol 1 wk. after reaction. Drowsy few hours later. Rash and fever 8 hrs. later. Temp. to 100·4 for 2—3 days. Pale rash for 2 days.
Temp. and pulse rise with morbilliform general rash.	Fever for 4 days 102·5 at peak.		Uneventful recovery.
	Fever for 2 days. 102 at peak.		Uneventful recovery.

FIVE CASES OF POST-INFLUENZAL ERYTHEMA NODOSUM

BY

Dr. VLADA BOGANOVITCH.

Physician in Anglo-Serbian Children's Hospital, Belgrade.

During recent years there has been much discussion regarding the ætiological factor in this benign skin eruption. Previously it had been the custom to look upon it as rheumatic in nature, and even yet some authors hold this opinion. It became apparent to most workers, however, that as a rule no history of a previous rheumatic manifestation could be obtained, and further that seldom was this the type of skin lesion which complicated arthritis. Erythema multiforme (erythema marginatum or circinatum) was the common variety.

As a result of the writings of Poncet[1], Pons[2], and Landouzy[3] the idea of its being of a tuberculous nature became prevalent. Pons reported that he found giant cell formation in the centre of a nodule; and Landouzy that he discovered a typical acid-fast bacillus in the lumen of a vessel in a nodule, and he concluded that the condition was the result of a tuberculous septicæmia. There is no doubt that a positive tuberculin reaction is found in a large proportion of the cases, but this does not of course prove that there is active tuberculosis present. It would, I believe, be remarkable, in view of the benign nature of erythema nodosum, if it were evidence of active tuberculosis. One must not forget that several authors (for example, Meare and Goodridge[4], Symes[5], Bronson[6],), have described active tuberculosis associated with it or following immediately in its wake, but these instances are rare.

Wallgren[7] records two epidemics of erythema nodosum. In one instance it affected four girls in one family at one time, and in the other three children simultaneously in a children's ward. As all the children had tuberculosis and apparently had been recently infected, this author inclined to the view that tuberculosis was a predisposing factor.

In America[8] the current opinion is that the disease is of streptococcal origin, but in England most authors to-day hold that it is probably the result of a reaction to many toxic substances. Lendon[9], however, described it as a specific infection under the title of 'nodal fever'.

In the present series of cases influenza would seem to be the predisposing, if not the exciting, factor. It may be that the influenza bacillus, as we know it does, opened the door to the streptococcus which as the Americans hold is the cause. The fact that in all of the cases here recorded the condition arose after the subsidence of the influenzal attack is rather in support of such a contention. Comby[10] in a series of 170 examples found influenza antecedent only 9 times. Influenza would not seem, therefore, to be a frequent precursor, and in this

connection it is interesting to record that in the Report of the Pandemic of Influenza[11] by the Ministry of Health there is absolutely no mention of erythema nodosum.

The negative reaction to the tuberculin skin tests in this series is also of interest, whatever view one takes of the significance of a positive test, for as previously mentioned this reaction is almost invariably positive in erythema nodosum. Pollak[12] found it positive in all of 48 cases, Moro[13] positive in 87 per cent. of 30 cases, and Bronson[6] found it positive in 4 apparently non-tuberculous children suffering from erythema nodosum.

Clinical report.

Case 1. D.S., male, aged 5 years. On the 13th February 1927, the father, a servant and one infant of one household developed influenza. Three days later the mother and the patient took ill. The illness in the patient commenced with pains in the back and limbs and frontal headache, slight shiverings and coryza, and rise in temperature which registered 38·1°C. Next day the temperature varied between 39·3° and 39·9°, the pulse was rapid but regular, the throat was red and the conjunctivæ hyperæmic, there were repeated epistaxes and an incessant dry cough with some dry râles over both lungs. Leucocytes numbered 8,300 per c.mm. Blood negative for malaria. Urine was scanty and contained abundant urates but no albumen, blood or sugar.

On the third day of illness temperature ranged between 38·5° and 39·2°, but headache and pain in back had disappeared. On 4th day patient had much improved : von Pirquet reaction was negative. On the 7th day of illness, though temperature was 37·6° the child looked exhausted and pale, bronchial râles were extensive, and on the internal aspect of both arms there had developed 2 roundish swellings of 3 cm. in diameter, of a bright red colour and tender to pressure. Two days later numerous swellings of a similar nature were present over the back. On the 10th day (Feb.25th) temperature was 37·1°. Swellings violet in colour. By March 7th child seemed perfectly well; all swellings had disappeared leaving in their place some pigmentation.

Case 2. B.C., male, aged 3½ years. The patient with his father, mother and two brothers took ill with influenza on Feb. 17th, 1928. In the patient the first appearance of the malady was cyanosis of the face, a feeling of coldness of the limbs, and repeated vomiting with diarrhœa. There was also slight delirium and the temperature registered 38·3°C. Next day temperature varied between 39·5° and 39·8°, the pulse was rapid, there was mental excitement with convulsions, repeated vomiting, diarrhœa, generalized hyperæsthesia and insomnia. He complained of headache and pains in the limbs and knees, the throat was red and the eyes injected. Examination of the chest and abdomen was negative. Leucocytes 9,600. Blood negative for malaria. Urine was scanty, showing abundant deposit of urates, but neither albumen nor sugar. On the 3rd day of illness temperatures 38·7° to 39·3°. Child still excitable with slight hyperæsthesia and profuse perspiration. On Feb. 20th the temperature was 38·3° to 39·1° and the child was drowsy and still sweating profusely, but by the next day the temperature was 37·2° and the patient seemed quite comfortable: von Pirquet reaction negative. On the 24th temperature was 36·1°, and the child again complained of pains in the limbs. Over the front of the limbs three rounded swellings about the size of a small nut and of a reddish colour were present. Two days later similar erythematous painful and tender swellings having the size of a pea were present over the anterior surfaces of both forearms and arms. Leucocyte count=6,800. On the 28th the child seemed feeble and pale ; but by March 9th all erythema had disappeared and child seemed quite well.

Case 3. D.B., male, aged 7 years, took ill along with his father, mother and two brothers on Jan. 17th, 1929. The onset of illness was characterized by violent headache, sub-orbital neuralgia, photophobia, muscular pains, especially in the calves, agitation, delirium and hyperæsthesia. Temperature 37·3°C. On the next day the temperature was 39·8°. Throat inflamed ; vomited repeatedly, restless and sleepless. Pulse very rapid, respirations rapid, but physical

examination of the chest negative. Still complained of headache and of pains in the calves. Urine showed a trace of albumen. Leucocyte count = 9,200; (myelocytes 3 per cent.) Blood negative for malaria.

On the 19th the temperature was 34·4°. Child was sleepless, restless, delirious, with extreme hyperæsthesia, vomiting and profuse sweating. Physical examination of chest negative. Spleen enlarged. Lumbar puncture :—fluid clear, 2 cells per c.mm., otherwise negative : von Pirquet reaction negative. On the 20th the temperature was 39·3°, and on the 21st 37·2°. Child then appeared quite comfortable, and on the next day the temperature was 37° and the boy was comfortable, eating and sleeping well.

On the 10th day after onset of illness (Feb. 26th) with slight diarrhœa and sub-normal temperature child was somewhat prostrated. On internal aspects of both legs and over the tibiæ there was present an eruption characterized by slight swellings, rounded, 5 cm. in diameter, of a rose-red colour, painful, tender and pitting slightly on pressure.

27.1.29. Still some diarrhœa, child crying all day on account of pain in the legs and refusing his food.

28.1.29. Temperature 37·1°. Diarrhœa better; patient was quiet, taking his food better and the erythema was less painful.

30.1.29. Temperature 37°. The erythema had become violet in colour, and was no longer tender on pressure.

10.2.29. Swellings have entirely disappeared leaving in their place some pigmentation.

13.2.29. Child seemed quite well.

Case 4. M.B., male, 7 years. In one family of seven members occupying a single apartment the father, mother and one child took ill with influenza at the same hour on Jan. 23rd, 1929. The patient took ill 36 hours later with fever, shivering, headache, repeated epistaxis, muscular pains, flushed face, hyperæmia of the conjunctivæ and inflamed throat.

On the 2nd day (Jan. 24th) his temperature was 39·2° to 39·5°C. Headache, epistaxis and muscular pains continued. Leucocyte count = 10,000 per c.mm., (myelocytes 7 per cent.). Blood negative for malaria. Urine was scanty, showing deposits of urates, but no sugar or albumen. Next day the temperature was 38·9° to 39·2° Headache had disappeared and throat was less red. Slight cough. Chest and abdomen negative. On Jan. 26th the temperature 37° and all pain had gone. On the 28th the child seemed better: von Pirquet reaction was negative. Leucocytes count = 7,000 per c.mm. No myelocytes. On Feb. 2nd the child became suddenly pale and refused his food. He complained of coldness of the limbs and was very agitated. Temperature subnormal, and on the next day two round hard swellings of a reddish colour and very tender to pressure were present over the front of the thighs. Temperature 37°. By Feb. 4th the child seemed better. He was less agitated, ate well, but still complained of pains in the legs, especially in the region of the erythema. On the 6th three similar erythematous swellings were present on the anterior surface of each forearm. By Feb. 12th the child was well and all pain had gone. By the 15th the swellings had disappeared leaving only pigmentation.

Case 5. K.P., boy, aged 7½ years. On Jan. 28th,1929 in a two-apartment house occupied by the parents and seven children, two of the children and the mother contracted mild influenza. On the next day the patient suddenly stopped playing, complained of pain in the head, tiredness and severe abdominal pain. He refused food and vomited 6 or 7 times, the face was flushed and the eyes watering. He had a cough and the throat was red. On the 30th his temperature 39·1° to 39·5°C. Headache, bilious vomiting and abdominal pain were still present. Dry râles were heard over both lungs and spleen was enlarged. Blood :—leucocytes 12,000 per c.mm. (myelocytes 3 per cent.) ; negative for malaria. Urine was scanty and contained neither albumen nor sugar. On the 31st the temperature was 39·2° to 39·6°. Abdominal pain had gone. Still slight vomiting and cough. On Feb. 1st the temperature was 39° to 38° and the boy was sweating.

Feb. 2nd. Temperature 37°. Cough practically gone, chest clear on examination.

Feb. 5th. von Pirquet reaction negative. Blood :—leucocytes 7,300, no myelocytes.

On Feb. 6th vomiting and diarrhœa returned with prostration and sleeplessness. Temperature 37·6°C. On inner aspects of legs there appeared an eruption of the nature of rounded painful swellings, 3 cm. in diameter, firm in consistency and of a bright red colour. On the 7th the temperature was 37·2° to 37·3°. Boy was still sleepless, agitated and with pain in the limbs

Feb. 8th. Temperature 36·9°. Diarrhœa was still present but pain had gone, though limbs tender to pressure. Eating and sleeping well.

Feb. 9th. Child was better. Limbs were still tender but less so than yesterday.

Feb. 12th. Child seemed perfectly well. Erythema had almost entirely disappeared.

Feb. 17th. Erythema had completely disappeared, only leaving pigmentation. Slight pain in both knees.

Feb. 21st. Articular pain still present on and off.

By Feb 27th the articular pain had gone, and by March 12th the child was perfectly well.

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STREPTOCOCCAL ALLERGY IN ACUTE RHEUMATIC INFECTION.

BY

RONALD A. MACDONALD, M.B., Ch.B., D.P.H.

Assistant Pathologist and Research Fellow (The Ida Sebag-Montefiore Research Fellowship), Hospital for Sick Children, Great Ormond St., London.

The ætiology of rheumatism has engaged the attention of bacteriologists for many years, and yet it is impossible to say that any definite conclusion has been reached. Many authors have suggested various types of non-hæmolytic streptococci as possible causes, but none of their claims has been definitely established, and the vast amount of literature that has accumulated does not bring us much nearer a solution to the problem. It is our intention to review a small portion of this literature, adding the results of certain investigations of our own, and to endeavour to explain some of the anomalous findings, on the supposition that there is no one definite streptococcus that is the cause of rheumatism, but that the disease is a manifestation of hypersensitiveness (allergy or hyperergy) to streptococci in general, and that in suitable circumstances any streptococcus may become the infecting agent provided the necessary degree of hyper-sensitiveness has been attained.

We propose first to examine some of the sources from which micro-organisms have been obtained, and the bacteriological findings in each case; then to discuss the question of allergy, and some of the experimental work that has been done on it; and finally to apply this theory to rheumatism, using it to explain some of the bacteriological difficulties in the disease.

Bacteriological investigations.

(a) **Tonsils.**—Attention has been directed consistently and for many years to the tonsil as a focus of infection, and any authors who have described 'rheumatic streptococci' have always been able to isolate them from the tonsil. On this account an investigation was undertaken in the hospital to see if there were any cultural differences in their streptococcal flora between rheumatic and non-rheumatic tonsils.

The tonsils selected were removed in the casualty department, and sent up to the laboratory with the minimum of delay. The rheumatic series was taken from all types of rheumatism, including chorea and old-standing carditis, the control series being from cases from which no history of rheumatism could be elicited. Immediately on receipt the tonsils were washed twice in sterile normal saline and dissected, and swabs taken from the bottom of the crypts. The swabs were then placed in tubes of broth (2 c.cm.) and thoroughly rinsed out. One or two loopfuls, according to the turbidity of the resulting emulsion, were spread out on chocolate agar plates and incubated for 48 hours. For the first half of the series 5 per cent. boiled blood-agar was used, but later Crowe's[1] medium was adopted. This medium is ideal for differentiating streptococcal colonies, as it shows morphology and peroxide formation better than any other.

After incubation a general survey of the relative numbers of colonies on the plate was made, and then a single colony of each streptococcocus was picked off under a binocular dissecting microscope (×10), and its appearances noted. The colonies were placed in tubes of heart-digest broth and incubated for 24 hours. With the resulting growths the following tests were carried out:—naked eye appearance of the growth in broth, morphology in liquid and solid media, growth at 20°C. in lactose gelatin, sugar fermentation (saccharose, lactose, raffinose, inulin, salicin, mannite and the effect on milk), heat resistance (5, 10, 20, 30 minutes at 60°C.),hæmolysis and bile solubility. Each organism was subcultured on Crowe's medium to determine if it were pure, or if its appearance had altered on subculture; the appearances of the colonies were described minutely after 2 and 5 days' incubation. Hæmolysis was tested for by adding 10 drops of the 24 hour broth culture to 10 drops of a 5 per cent. suspension of washed red blood corpuscles in normal saline in a Wassermann tube, incubating for 2 hours, and leaving overnight in the ice chest. By this means the amount of hæmolysis could be noted in the same way as in the Wassermann reaction, reading 4, 3, 2, 1, 0, according to the amount of cellular deposit, and the colour of the supernatant fluid. This method was found to be very accurate and, as little difference was seen between cultures and centrifuged supernatant fluids, also very rapid, since the same broth culture could be used as for the sugars. Human corpuscles were employed for the most part, as a parallel series showed them to be rather more sensitive to hæmolysis than sheep's corpuscles, though less susceptible to darkening or methæmoglobin production.

The complete results of all the tests are given in Table 1.

The most striking thing in this comparative series (Table 1) is the extraordinarily similarity between the rheumatic and the control figures. In no single particular, except perhaps the number of streptococci isolated per tonsil, is there any material difference. Nor indeed was there, as a rule, any marked difference between the appearance of a plate from a rheumatic and a non-rheumatic tonsil, looked at generally; and even on Crowe's medium it was impossible to tell if any given plate was from a rheumatic or a control tonsil. In some cases practically pure growths resulted from both types of tonsil, but these were quite indiscriminate and might in either series be green, non-green, or hæmolytic. Most observers who have described rheumatic streptococci have placed them in the non-hæmolytic and non-green-producing group, and therefore in a series of this nature we might reasonably expect to find this group preponderating in the rheumatic series. Once again, however, there is little difference, the rheumatic being slightly lower. This accords well with the work of Hitchcock[2], who found no greater incidence of inert streptococci in rheumatic fever throats than in others.

(b) **Teeth, nasopharynx, etc.**—With regard to the mouth, teeth and nasopharynx, not nearly so much work has been done, but at the same time some authors believe that they play as important a part as foci of infection as do the tonsils. Rolleston in 1910 said that he considered patients with oral sepsis specially prone to relapses of rheumatic fever, and Langmead[3] (1920) mentions throat, nose, mouth, nasopharynx and bowel as possible sources of infection. Shaw[4] in 1925 showed a parallel between the incidence of diseases of the mouth, teeth, gums and fæces, as apart from tonsillitis, and that of rheumatic fever. Fordyce[5] (1927) agrees with Langmead in suggesting the treatment of carious teeth, adenoids and constipation, as well as tonsils, with a view to removing focal infection.

(c) **Fæces.**—Langmead and Fordyce both mention the bowel, and other suggestions have been put forward with regard to the part it plays in rheumatism. There is very little literature dealing with the bacterial flora of the

TABLE 1

COMPARATIVE SERIES OF RHEUMATIC AND CONTROL TONSILS

		Rheumatic	Non-rheumatic
Total no. of tonsils		50	48
Total no. of streptococci		190	150
Average no. of varieties of streptococci per tonsil		3·8	3·3
Types	Hæmolytic	14%	14%
	Non-hæmolytic	86%	86%
	Green producers	46%	46%
	Non-green or inert	51%	53%
	Doubtful	3%	1%
By sugar reactions	Str. mitis	44%	37%
	„ salivarius	26%	28%
	„ pyogenes	12·5%	11·5%
	„ fæcalis	4%	3%
	Other streptococci	13·5%	20·5%
By Crowe's colour grouping	Grp. A. No colour	26%	23·75%
	„ B. Yellow	27%	28·75%
	„ C. Green	32%	28·75%
	„ D. Black	1%	2·5%
	Hæmolytic	14%	16·25%
Growth in broth	Clear	42%	42·5%
	Turbid	56%	56·5%
	Doubtful	2%	1%
Chain formation	Medium and long chains	37%	41%
	Short chains, pairs and clumps	63%	59%

bowel in rheumatism, and therefore we have examined a small number of specimens of fæces in the same way as we did the tonsils. As before, swabs were taken from the fæces, emulsified in broth, and the emulsion plated out on Crowe's plates. Similar reactions were carried out with pure growths of the resulting colonies. In this series the cases were all in hospital, and were mostly acute joint or cardiac conditions, with one or two cases of chorea.

The first point to be noted in this series is that there are definitely more varieties of streptococci in the rheumatic specimens than in the non-rheumatic. This is confirmed by looking at the plates, which show in general more numerous colonies of streptococci in the rheumatic series. The next point is the increase of green varieties in the rheumatics, and at the same time the reduction in the heat-resisters. This rather suggests that more of the mouth types were present in the rheumatic bowel. One striking point is evident in both series, namely, the small proportion of true fæcalis types, as judged by

TABLE 2

COMPARATIVE SERIES OF RHEUMATIC AND CONTROL FÆCES

		Rheumatic	Non-rheumatic
Number of specimens		14	14
Number of streptococci isolated		61	46
Average no. of strep. per specimen		4·4	3·2
Types	Hæmolytic	—	—
	Green-producers	51%	36·5%
	Non-green-producers	49%	63·5%
By Crowe's colour grouping	A.	47·5%	61·5%
	B.	9·0%	8·0%
	C.	42·0%	28·5%
	D.	1·5%	2·0%
Mannite fermenters		26·5%	28%
True fæcalis types		13·0%	15·0%
Heat resistant types	5 min. at 60°C.	15·0%	13·0%
	15 min. at 60°C.	5·0%	4·0%
	30 min. at 60°C.	15·0%	28·0%
	Non-resistant	65·0%	55·0%
By sugar reactions	Fæcalis group	26·5%	28·0%
	Mitis group	61·0%	57·0%
	Salivarius group	5·5%	15·0%
	Others	7·0%	—

the classical features of morphology, heat-resistance and mannite fermentation. By far the commonest streptococcus is one of the mitis type, which is not heat-resistant.

Mention must be made at this point of the differences between solid and liquid specimens. We asked for liquid specimens to be sent, but in all cases this was not possible, and a definite difference was noted between the two. In the first place, the percentage of streptococci as compared with B. coli and other organisms was considerably lower in the solid specimens. Secondly, these contained more fæcalis types. This seems to show that the streptococcal flora of the bowel alters in accordance with the level from which the specimen comes. Naturally our series is too small to allow us to be dogmatic, but the alteration in bowel content, and the increase of streptococci in the rheumatic series, are sufficiently striking to warrant further investigation. Apart from these points there is little difference between the two series, and though the rheumatic group contained more varieties of streptococci in each specimen, no particular types preponderated, and as far as we could make out, there were no types present in the rheumatic series which were not at some time or other also isolated from the control series.

(d) **Blood and post-mortem cultures.**—Blood cultures in acute rheumatism are notoriously unsatisfactory on account of their being so frequently negative, even in cases with high temperatures. Lynch[6] (1924) draws a distinction between the very small number of positives in acute rheumatism, and the large number in bacterial endocarditis. Swift and Kinsella[7] (1917) found less than 10 per cent. positive in their series of blood cultures, and of the strains of streptococci found in these 10 per cent., none bore any relation to one another, or to any isolated elsewhere. Jones[8] (1928), using a very full technique, found only one positive in 33 cultures. Our own cases accord with these findings, no positives being obtained in the last 20 cultures, except in cases of bacterial endocarditis, where green streptococci have nearly always been present.

Cultures from heart valves, myocardium and pericardial fluid have, as a rule, been more successful, and in the few cases which we have had an opportunity of culturing, streptococci have nearly always been isolated. The possibility of contamination must not, however, be overlooked in interpreting these findings, as streptococci of the fæcalis type, and even occasionally others, are sometimes present in pericardial fluid and heart blood, where their presence is entirely accidental. Recently we have been adopting the technique of flaming pieces of heart muscle or valves in spirit, and then excising, with aseptic precautions, a piece from the inside of the slightly scorched specimen. In this way we have isolated streptococci pure in two cases, one having a green-producing short-chain streptococcus of the mitis type, and the other two non-hæmolytic and non-green varieties. Zinsser[9] (1928) mentions that he also found two distinct types of streptococcus in heart muscle from an authentic case of rheumatism, a point of definite importance when considering a specific streptococcal ætiology for the disease.

(e) **Joints and nodules.**—Here again attempts at isolation of organisms have been almost uniformly unsuccessful. As regards the joints, this is not surprising in a disease which never produces suppuration, and in which the inflammation flits about from joint to joint. In one or two cases positive findings have been reported, but the diagnosis in these cases has not been well established. Crowe[10], however, has described what he has named osteotropic streptococci, which have a special affinity for bone tissue, and on intravenous injection into rabbits will settle down under the articular surfaces of some of the larger bones. Though he is dealing with osteo-arthritis in his paper, it is possible that organisms may be localized temporarily in this position in more acute conditions, in which case the negative findings in joint fluid could be explained. We shall refer to this point again in the discussion.

Skin tests.

A considerable amount of work has been done on skin tests with non-hæmolytic streptococci, using the same technique as in the Dick test, and a fair amount of success has been met with. Birkhaug[11] (1927) produced a soluble exo-toxin from his non-methæmoglobin-forming streptococcus, with which he performed a large number of skin tests, obtaining a considerably higher percentage of positives in rheumatic patients than in others. Later[12]

in 1929 he summarized the results of tests done in various parts of Europe on 594 individuals. His results were as follows :—72 per cent. positive to non-hæmolytic streptococcal products in active rheumatism, with 64 per cent. positive to boiled streptococcal filtrates. In non-active cases his figures were 64 per cent. and 25 per cent. respectively, while in non-rheumatic controls he obtained only 14 per cent. of positives. Kaiser[13] (1928) using Birkhaug's original toxin at 1 in 100 strength found 32 per cent. of all children positive, 20 per cent. where there was no history of rheumatism, 35 per cent. in cases of repeated sore throat, and 72 per cent. in cases with a history of rheumatism. Swift, Wilson and Todd[14] (1929) did skin tests with green and non-green streptococci, and found a greater number of positives in active than in inactive or cured cases ; that boiled filtrates were less positive in inactive cases, and that generally rheumatic patients gave more positives than others. They also found no correspondence between Dick tests, and tests with non-hæmolytic streptococci. Edith Jones[8] (1928) found hyper-sensitiveness in rheumatic fever patients to a large variety of non-hæmolytic streptococci as evidenced by positive skin reactions with filtrates of these strains. Howell and Corrigan[15] (1928) obtained a relatively high percentage of positives with many types of streptococci in children, which they describe as susceptible to streptococcal infections in general.

Comparatively little work has been done in this hospital with skin tests with non-hæmolytic streptococci, but a small number of children have been tested with various strains. The numbers of positives have not varied much with the organisms employed. It would seem that there is some definite hyper-sensitiveness to streptococcal products which can be revealed by skin tests, but the difficulty at present is that the optimum method of preparing the products, and the organisms from which to derive them, have not yet been decided. Recent work tends to point to autolysis as being an important step in the preparation of a toxin, and that organisms which autolyse easily, and therefore liberate their proteins, are more potent than others, irrespective of their origin or supposed pathogenicity.

Animal experiments.

The literature on this subject is immense, as nearly every one who has worked at the bacteriology of rheumatism has tried to reproduce the clinical picture of the disease in some animal, usually the rabbit. What is more, considerable success has been met with in the experiments, some degree of arthritis, and often of the non-suppurative variety, having been produced in very many instances. Poynton[16] in 1904 was able to produce arthritis and carditis in rabbits and monkeys, with cultures of his diplococcus from a fatal case of rheumatic endocarditis ; and from then onwards to the present day most authors, including Beattie[17] (1906), Coombs, Miller and Kettle[18] (1912), Faber[19] (1915), Small[20] (1927), Birkhaug[11] (1927) and a host of others have repeated this with the organisms they isolated. Most of the workers used large doses which were in many cases injected intravenously, thus possibly accounting for the slight differences between the resulting pathological pictures and those of human rheumatism.

Though this production of a fairly typical arthritis in animals would seem to fulfil one of Koch's postulates, yet by no means all the experiments were performed with the same organism, and coincidently with them arthritis was produced by streptococci which had no possible connection with rheumatism. Cole[21] (1904) found lesions in rabbits injected with ordinary alimentary S. fæcalis and salivarius identical with those from 'rheumatic' streptococci. Gordon[22] (1912) agrees with this, and Jackson[23] (1913) found no striking differences in the reactions in rabbits to different types of streptococci, and Henrici[24] (1916) endorses this view. Rothschild and Thalhimer[25] produced arthritis in about 50 per cent. of their rabbits by inoculation with a considerable variety of streptococci. Topley and Weir[26] (1921) point out that though lesions similar to human rheumatism can be produced by inoculation with streptococci from acute rheumatic cases, similar lesions can be produced by streptococci from widely different sources.

Discussion on allergy.

(1) **Introduction.**—There are four main points to be observed on looking through the bacteriological findings from these various sources, and the results of skin tests and animal experiments.

(1) That the ætiology of rheumatism is intimately connected with streptococci;

(2) That authors who have described streptococci have not been able to place them in one cultural, morphological, bio-chemical or serological group;

(3) That positive skin tests have been obtained in cases of rheumatism with the products of many different non-hæmolytic streptococci;

(4) That unrelated streptococci, from various unconnected sources, have been as successful in producing experimental arthritis in animals as have those from cases of rheumatism.

These last three points make it very difficult to attribute rheumatism to one definite streptococcus, and yet with the exception of Achalme[27] and his adherents, who describe a bacillus resembling anthrax, Clarke[28] who suggests the rat flea as a possible carrier, and one or two authors who suggest filterable viruses, observers are unanimous in laying some blame on streptococci. That these organisms are normally present in all human beings naturally complicates the issue, and the ease with which many varieties of streptococci can be isolated from the tonsils, mouth, fæces, etc., makes their ætiological relationship more difficult to prove. It is to these normal harbours of streptococci that attention has mainly been directed with a view to eradicating focal infection, and the consequent absorption of toxins. In the case of the tonsil, this has been the main reason advanced by the large number of eminent authorities who recommend tonsillectomy in rheumatism. Yet, in spite of the undoubted value of this measure, there is, as our experiments show, a complete absence of any difference in the streptococcal flora of rheumatic and non-rheumatic tonsils. Again in the case of the intestine, one may find any streptococcus in the fæces of rheumatic or non-rheumatic cases, and very little difference between them, yet attention to the bowel is

frequently advocated as a useful line of therapy in rheumatism. Vaccines also have given good results in some hands, and have been useless in others, and also in more chronic cases the removal of septic focci has been of great value in one case, and valueless in the next. How then are we to reconcile these conflicting results ? It must be obvious that, if one definite streptococcus were the cause of rheumatism, these anomalies could not have arisen, even though the classification of the non-hæmolytic streptococci is sufficiently difficult to have made it uncertain to which group the organisms isolated may belong. With modern methods, such as the use of differential media and serological tests, some similarity should have been observed between the numerous streptococci which have been found in rheumatic lesions. This has not been done, however, and recent work shows more and more varieties isolated, and these and others from non-rheumatic sources capable of giving positive skin tests and producing arthritis in animals.

Let us suppose then that all these organisms can produce rheumatism. If this is accepted, the multiplicity of results can be explained quite easily. It remains, then, to see how all these varieties can be related to the disease. Gordon[22] in 1912 suggested that rheumatism might be an auto-infection or auto-inoculation by streptococci of the normal alimentary canal, induced by exposure, damp or lowered resistance. This is a very general statement, but if we make it more specific by suggesting that this auto-inoculation is really the production of hyper-sensitiveness it brings this early statement into line with later work. Harrison[29] (1913) came to the conclusion that there were two alternative explanations of rheumatism, either that more than one streptococcus is responsible, or that cultural and other characteristics are not sufficiently well defined to enable one to separate rheumatic from other streptococci. We have already mentioned this latter possibility, but do not consider that it is now tenable.

(2) **Experimental work.**—Faber[19] (1915) was among the first to suggest hyper-sensitiveness. He injected joints with dead bacteria and, when the resulting inflammation had settled down, he found that a dose of organisms too small to produce any result in an untreated joint, when injected intravenously, would produce arthritis in this joint. This question has been more fully worked out recently, both with streptococci and with other organisms. Zinsser and Grinnel[30] (1927) produced a condition of allergy in guinea pigs by repeated injections of a pneumococcus autolysate; and Freiberg[31] in 1929 succeeded in inducing a proliferative arthritis in rabbits by repeated injections of B. dysenteriæ Flexner, and says that he considers arthritis to be a local allergic manifestation of a generalized state of allergy to a specific bacterium or bacterial extract. With streptococci, as early as 1923, Bristol[32] discussed the hypothesis that scarlet fever is a hyper-sensitive state, and compares it closely with drug and serum allergy. Mackie and McLachlan[33] (1927) produced a hyper-sensitive state in guinea pigs to scarlet fever toxin, and say that this state is not specific. Dochez and Stevens[34] did the same with rabbits and erysipelas filtrates, and at one phase, could neutralize the condition with erysipelas immune serum. They also consider the rash of scarlet fever and the Dick reaction to be allergic manifestations.

Turning to rheumatism and hyper-sensitiveness to non-hæmolytic streptococci, Birkhaug[11] (1927) suggests that a toxin produced by a group of serologically unrelated streptococci may produce rheumatic fever by its prolonged fixation in the tissues. Subsequently[35] (1928) he sensitized rabbits and guinea-pigs to toxins from various streptococci by giving repeated doses, and demonstrated the sensitiveness by positive skin tests in these animals which had failed to react before. In this paper he says that it is difficult to attribute the many variable manifestations of rheumatism to the action of a single micro-organism. In 1929[12] he explains his positive skin tests purely on the grounds of allergy, saying that there is a non-specific allergenic factor present in products of inert and viridans streptococci to which rheumatic patients react hyper-ergically. Swift, and his co-workers have done a great deal of research on this subject. Swift, Derick and Hitchcock[36] (1927) produced allergic tuberculin-like reactions in patients after inoculation of killed streptococci or their products, and a slow febrile response, at its height in 20-24 hours, much later than non-specific protein shock. Andrewes, Derick and Swift[37] (1926) take this subject further ; in rabbits, they showed, with intradermal injections of green streptococci, lesions which reach their height in 24-48 hours, retrogress and then show a secondary reaction about 8 or 9 days later. Many streptococci, and occasionally pneumococci, produce this reaction, but not hæmolytic streptococci, staphylococci, B. coli or M. catarrhalis. This secondary reaction is not due to increased activity of the organisms, as the lesions are sterile, and dead organisms can produce it as well as living ones. A second injection within 9 weeks of the first, is not followed by this secondary reaction, and this inhibition is not specific among non-hæmolytic streptococci. These experiments are suggestive, and can hardly be explained except on a basis of allergy. Derick and Swift[38] (1927) deal further with the hyper-sensitive state, mentioning that it can be increased up to a point by inoculations at 5-10 day intervals, and seems to depend on some lesion or focus in some part of the body. This may be produced experimentally by means of an infected agar tumour, (Crowe[10], 1929), which liberates continually a supply of allergizing material.

An interesting contribution to this subject was some work done by Hanger[39] (1927). He tested rabbits and found that, as a rule, they reacted negatively to streptococcal antigens, as judged by skin tests. Rabbits have relatively few Gram-positive organisms in their nasopharynx, but relatively numerous Gram-negative bacilli, notably B. leptisepticum. Rabbits react, in the main, positively to filtrates from these bacilli, which emphasizes the importance of sensitizing foci in the body. Later he says that any rabbits which lack this sensitiveness to B. leptisepticum can have it developed by infecting the skin with a virulent culture of the organism. Allergic rabbits die when 1 c.cm., or even less, of filtrate is given intravenously, while non-allergic rabbits will resist 15 c.cm., and immune rabbits even more. He also says that these reactions are non-specific. Swift, Derick and Hitchcock[40] (1928) have obtained identical results with streptococci, being able to produce hyper-sensitiveness and immunity in the rabbit by varying their doses of non-hæmolytic streptococci, and their methods of administration. In the hyper-sensitive rabbit, a moderate dose of

organisms produces death, or very severe lesions; in the normal rabbit a relatively slight lesion ; and in the immune rabbit no effect.

(3) **Definitions of allergy.**—We have described above some of the recent experimental work on allergy. Let us now try to show exactly what allergy is. Swift and Derick[41] (1927) give an account of the condition as follows. :—

> Hyperergy to non-hæmolytic streptococci is an early stage of resistance in which there is a maximal response of the tissues to a minimal stimulus. It is the result of the action of the antigen—the streptococci—in a limited area represented by the focus, where tissue destruction occurs. It may indeed depend upon substances arising in such a focus. Complete or efficient immunity, on the other hand, is an optimal response to a maximal—within certain limits—stimulus, and is the result of the action of the antigen over a wide area without the induction of focal tissue destruction.

Zinsser[9] (1928) says much the same thing in describing allergy as

> an increased capacity of the tissues to react to an antigen which may come to the body as a new infection, or through the lighting up of an old focus. This increased capacity to react may be injurious, and result in pathological changes and disease. On the other hand, in its deeper pathological significance, it probably means merely that the tissues, through specific sensitization, are on a hair trigger and can respond both cellularly and humorally to this antigen with a speed and vigour not possessed by the normal body. In this sense the allergic state may in certain instances be regarded as an index of resistance, a thing which we believe to be true in the case of tuberculosis. It is probable that, in order to produce any sort of noticeably acute pathological change in the tissues of a sensitive animal, it is necessary that the antigen shall reach the tissues in a relatively concentrated state. This seems indicated by our own experience in obtaining violent hæmorrhagic skin reactions with pneumococcus autolysate in guinea pigs, which reacted hardly at all when the same and larger amounts of antigen were distributed over the entire peritoneum by intra-peritoneal injection. It may also be that the situation is complicated by local degrees of sensitiveness of individual tissues—a view which experiments in rheumatism encourage.

(4) **Application of the theory of allergy to the bacteriological problems of rheumatism.**—Finally, let us link up these suggestions with the bacteriological findings described in the earlier part of this paper, and try to explain some of the anomalous facts in this way. In the first place, the lack of cultural and serological uniformity among the streptococci isolated from cases of rheumatism is easily explained. Most of the authors whom we have quoted in this discussion emphatically state that the hyper-sensitiveness that they have found or produced is not specific, and that any non-hæmolytic streptococcus, whether recognized as pathogenic or not, may, in suitable circumstances, induce the allergy ; also that one streptococcus may be used to produce this state, and another to demonstrate its presence by means of skin reactions. Why then have some experiments with non-hæmolytic streptococci failed to produce an allergy, or give positive skin tests in hyper-sensitive patients ? An explanation for this has been suggested in the fact that autolysis of the streptococci is the important factor in yielding allergizing material, and certainly autolysates of streptococci have been more potent than mere filtrates. It has also been suggested that some streptococci, including Birkhaug's RF1 strain, autolyse more readily than do others, and are therefore more potent. This autolysis naturally would go on more rapidly in a focus of infection where organisms are continually being destroyed by the body, than in a culture where they are living in their optimum conditions, and therefore natural autolysis and consequent liberation of allergizing material is more potent than the inoculation of cultures in experi-

mental animals, except perhaps in the case of the infected agar tumour method. It is not presumed for a moment that this is the whole story, for when dealing with antigens we are trying to reproduce a single condition with a very complex organic substance, and we have yet to learn what fraction of the bacterial protoplasm is responsible for what effect. Thus it is probable that the experimental success of some workers with the organisms they isolated may be due to their having found organisms which autolyse easily, or that they have accidentally included the correct antigenic fraction, and not to any specific ætiological rôle in respect of those organisms.

Septic tonsils, and even indeed normal tonsils to a less extent, form very good foci from which a supply of this allergizing material can be liberated, which explains the undoubted value of tonsillectomy in rheumatism. In the same way foci of infection in other situations, such as the mouth, teeth, bowel, etc., probably liberate this allergizing material, and attention to these situations should be, as indeed it is; a useful therapeutic step. This conception is not very far removed from the older one, namely, that removal of these foci exercised its beneficial effect by removing sources from which organisms and their toxins might be diffused through the body. Probably organisms, and at any rate toxins, are occasionally disseminated through the tissues, but more important is the diffusion of allergizing material.

Inflammation of the joints, which is one of the chief manifestations of rheumatism, is somewhat analogous to serum sickness, an established allergic condition. If, then, we explain rheumatism on a basis of allergy, the sterility of the joint fluids is not surprising. There is also, of course, as mentioned above, the possibility of organisms being present in the bone under the articular cartilages. That allergy may enter into this question also is suggested by some of Crowe's[10] experiments. He kept one of his osteotropic streptococci on ice for three weeks, and on injecting it into a rabbit, found it had lost its osteotropic properties. He then infected an agar tumour in a rabbit with this organism, and injected three days later a small quantity of the organism intravenously. Seventeen days later the rabbit was killed and this organism again isolated from the bone, suggesting that the infected agar tumour, by liberating allergens, had so increased the sensitivity of the animal that the organism could again settle in the bone.

On a hypothesis of allergy can also be explained the sterility of nodules and blood. The occasional positive blood cultures, and the presence of streptococci in heart muscle, are not entirely contradictory, for in the hypersensitive child, though the disease can exist in their absence, organisms may easily escape into the circulation, and hence to the tissues. It is also possible that the cases in which blood cultures are positive may form a link between acute rheumatism and bacterial endocarditis, a condition which frequently follows on rheumatism and in which blood cultures are almost invariably positive. In these cases the generalized presence of the antigen may lead more nearly to the 'optimal' response, in place oft he 'maximal' response of the local presence of the antigen, and thus explain the comparatively prolonged nature of bacterial

endocarditis. That some immunity is developed is proved by the fact that definite agglutination, often to a fairly high titre, can be demonstrated in the patient's own blood to his own organisms.

Another point which fits in with the theory of allergy is the fact that children rarely develop rheumatism before the age of four years. Vining[42] (1925) describes the condition of the pre-rheumatic child, and states that rheumatism in children is preceded by a period of months or years of ill-health. It arises in the 'debilitated toxic child.' Is it not possible that this is the period in which the child is becoming sensitized to the streptococci which are normally or abnormally present in its body? Mackenzie and Hanger[43] found that infants nearly all gave negative skin reactions to products of various streptococci, even though their mothers reacted strongly: a fact which suggests that the infants had not yet had time to become sensitive.

Summary.

(1) Some of the literature describing streptococci isolated from various situations in rheumatic patients is reviewed, and our own results added.

(2) A series of tonsil cultures from rheumatic and non-rheumatic cases is given, showing practically no differences between them with regard to the streptococcal flora.

(3) A similar shorter series of fæces showed a greater average number of types of streptococci per specimen, and a larger percentage of green streptococci in the rheumatic specimens. Apart from this, and a slight diminution of heat-resistant types in the rheumatic series, there was little difference between them.

(4) Some of the work that has been done on allergy in rheumatism is described, and a definition of the condition is quoted from two authors.

(5) Some of the bacteriological and other anomalies of rheumatism are explained on a basis of allergy.

We would like to acknowledge our indebtedness to Dr. D. N. Nabarro, Director of the Pathological Department, for his advice and encouragement during this work, and for his kindness in correcting the proofs; to the honorary and resident staff for furnishing specimens from their wards; and to the casualty department under Mr. Crooks and afterwards Mr. Keogh, for sending tonsils removed at operation.

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A CASE OF ENTEROGENOUS METHAEMOGLOBINAEMIA (?CONGENITAL) IN A CHILD

BY

REGINALD MILLER, M.D., F.R.C.P.

Physician, Paddington Green Children's Hospital, London.

Enterogenous methæmoglobinæmia, a comparatively rare disorder in adults, has never, so far as I am aware, been described in a child, although Prof. L. G. Parsons[1] has recorded a case of sulphæmoglobinæmia in an infant of nine months old. For this reason the following case is recorded.

P.B., female, aged 9 years. She was first seen in April, 1927, when she was brought to the out-patient department at the Paddington Green Children's Hospital for bronchitis. Her obvious blue colour was explained as being due to congenital heart disease, but as it did not resemble the cyanosis of that condition, she was admitted for investigation.

The girl had lived in an institution for the past two years and it was impossible to get into touch with her mother or father. From the age of nine months until she was admitted to the institution, she was under the charge of a foster-mother. This woman when interviewed stated that the child was blue when she first took charge of her, and that she had always understood that the blue colour dated from birth and was due to congenital heart disease. The colour had remained the same all the years she had had charge of the child, and it had not altered while in the institution from which she was brought to hospital.

The girl's health was stated to have been good except for obstinate constipation and a tendency towards abdominal distension. Although it was understood that her colouration was due to cardiac abnormality, it was realized that apart from this one symptom the heart's condition seemed to do no harm to the child.

First Admission. Admitted in April, 1927, the girl was well grown and developed for her age (9 years). Her face and body were plump. Her hair was light brown, and her eyes pale blue. Apart from her cyanosis she appeared in good health. She was, however, persistently and severely constipated, and her abdomen was rather distended but only to an extent suggestive of constipation.

The blue colour of the child was very obvious at any time and was increased when she became flushed or hot. The tint of the blueness was not the same as that of cardiac cyanosis, having a more leaden or steel tinge in it. The extremities, although blue, were quite warm; the tips of the ears were not cyanosed. The white skin, as of the abdomen, was of a colder white than in an ordinary child.

The heart showed distinct enlargement of the left ventricle. The apex-beat was ¾-inch outside the nipple line and was rather thrusting in character. A skiagram confirmed this. The pulse was good. There was no trace of dyspnœa on exertion. There was no clubbing of the fingers. The blood showed no erythrocytosis. The red cells numbered on several counts between 4½ and 4¾ millions. The leucocytes numbered about 6,500; and the hæmoglobin which was estimated with difficulty owing to the peculiar tinge of the blood, stood at about 80 per cent. The colour index was ·9.

The abdomen was full and rather distended, but to no very remarkable degree. Nothing abnormal could be detected on palpation. An opaque enema showed that the colon was large and easily distended, but was nothing like the voluminous colon of megacolon. An enema of two pints was very easily delivered and retained by the child. Without treatment, the bowels never acted. The stools showed no signs of undigested food or colitis, but were rather abnormally offensive. Bacteriologically there was at first found a great excess of streptococci of the common fæcal type over B. coli, but after a course of colon lavage this excess largely disappeared. The 'nitroso-bacillus' could not be found in three examinations. The only abnormality in the urine was the very large amount of indican which was constantly present. The child's temperature was regularly raised to 99·5° or 100° at night.

A spectroscopic examination of the blood was kindly carried out for me by Dr. W. H. Hurtley at St. Bartholomew's Hospital who diagnosed the condition as one of methæmoglobinæmia on the following grounds :—

(1) A diluted solution of the blood showed a band to the left of the D line, at '3' on an arbitrary scale.

(2) This band disappeared when the blood was reduced with a trace of sodium hydrosulphite. (This is typical of methæmoglobin : the band of sulphæmoglobin would remain.)

(3) On the addition of ammonium sulphide the band at '3' instantly disappeared, while a band at '3·5' appeared slowly. (This is the band of sulphæmoglobin. The '3·5' mark is nearer the D line than is the '3' mark.)

(4) Sulphuretted hydrogen was passed into the diluted blood. This caused the '3' band to disappear immediately, and a sulphæmoglobin band at '3·5' to appear rapidly in its stead.

It was assumed that the three signs, methæmoglobinæmia, indicanuria and persistent low fever were interdependent, and attempts were made by various measures to influence them during the three months the child remained in hospital. Chief reliance was placed upon the regular use of large enemata of double normal saline in alkaline solution. These were given daily over a long period. Various so-called intestinal disinfectants were also tried, and a three week's course of B. acidophilus milk was given, the cultures for which were kindly supplied by Dr Laurence Garrod. All these measures were quite unsuccessful in influencing any of the three symptoms already mentioned. The alterations in the child's colour were not more than were ultimately learned to be due to the flushing or the pallor of her skin. The indicanuria persisted in spite of the prevention of any apparent constipation by the use of enemata, and the low fever was also uninfluenced.

The girl was discharged after a stay of three months in hospital.

Second Admission. The child was not seen again for nearly two years when she was sent for and re-admitted on March 8th, 1929. In the interval she had kept in her usual state of health and on re-examination no change in her condition could be found. Dr. Hurtley kindly re-examined the blood and confirmed his previous diagnosis.

At Dr. Morley Fletcher's suggestion daily colon douches of potassium permanganate (1 in 4,000) were started on March 23rd., and a careful watch was kept on the amount of indican in the urine. This began to lessen about April 8th, and an improvement in the child's colour was noted about ten days later. On April 30th, the urine became free of indican for the first time during all the weeks she had been under observation. It reappeared from time to time, but in small quantities only. The child's colour made a very definite improvement, so that when she was not flushed the abnormality of the complexion was hardly recognizable, but when heated by exercise her methæmoglobinæmic tint became again obvious. Improvement beyond this point could not be obtained. A course of completely vegetarian diet appeared to make no difference to the girl's progress.

As the child's colour improved it was noticed that her hair became lighter, giving rather the appearance of a child's hair which had been bleached in the sun. The variations in the indicanuria were observed to precede the variations in the colour of the child's complexion by about 24 to 48 hours. An increase in the indicanuria would be followed by an increase in the degree of cyanosis, and vice versa.

The girl was discharged on August 14th, 1929.

Summary.

(1.) A case of enterogenous cyanosis due to methæmoglobinæmia has been described in a girl first seen at the age of 9 years. The cyanosis was certainly present at the age of 9 months, and is said to have been present at birth. It was attributed to congenital heart disease.

(2.) Apart from the abnormal colour the girl appeared in good health. The absence of any symptoms of illness is perhaps to be attributed to the comparative absence of anæmia.

(3.) The heart showed an enlarged left ventricle: there was no erythrocytosis.

(4.) The methæmoglobinæmia was accompanied by obstinate constipation, excessive indicanuria and some persistent low fever at night. The degree of cyanosis varied directly with that of the indicanuria.

(5.) Considerable improvement, but by no means a complete cure, resulted from the daily use of enemata of potassium permanganate solution (1 in 4,000). Other measures appeared useless.

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AN UNUSUAL CASE OF CONGENITAL PYLORIC STENOSIS

BY

ROBERT E. STEEN, M.D., F.R.C.P.I.

The following case of hypertrophic pyloric stenosis presents two very unusual features: first, the advanced age of the infant; and secondly, the intermittent character of the symptoms.

Clinical report.

V.K., female, aged 7 months, was admitted to the Hospital for Sick Children, Great Ormond Street, under the care of Dr. Robert Hutchison on the 28th November 1928, suffering from vomiting, constipation and wasting.

HISTORY. 7 weeks premature infant. Normal labour. Birth-weight 5lb. Progress appeared to be satisfactory until 14 days old, when vomiting commenced. This was projectile in character, and frequently per nares. Constipation which had been present in a minor degree since birth now became severe. The stools were small and hard, and frequently none might be passed for 36 hours, and then only after the administration of an enema. The weight which had been increasing satisfactorily since birth now began to fall. Vomiting, constipation, and wasting continued with undiminished severity until the baby was 2½ months old, when these symptoms subsided suddenly and completely. The stools now resumed their normal colour and frequency, and the weight started to increase. This satisfactory state of affairs lasted six weeks, at the end of which time one large vomit occurred. A further fortnight passed with complete absence of symptoms, and then a second bout of severe vomiting commenced at 4½ months of age. Two days before the vomiting made its reappearance constipation again became severe and the parents stated that this gave them a warning that a relapse was about to occur. This second 'attack' lasted one week, during which the child again lost weight. A further fortnight followed during which no vomiting occurred, constipation disappeared, and the child rapidly gained weight. 8 oz. were gained in the first week and 10 oz. in the second, the weight at the end of this period being 8¾ lb. Everything suggested that the corner had been turned when at the end of the fortnight, *i.e.*, at 5¼ months, the third and final bout of vomiting began. Constipation again became severe and the weight fell steadily. This continued until admission 7 weeks later.

Child was never breast-fed. A large variety of foods were tried. At each change of food a temporary subsidence of vomiting occurred for one or two days.

One other child in family, female, aged 6, who had always been healthy. No blood relationship between parents.

ON ADMISSION. Very small wasted baby looking more like a 7 weeks than a 7 months infant. Weight 5 lb. 9 oz. Fontanelle sunken. Well-marked visible gastric peristalsis seen. The pyloric tumour was felt far out, nearly in the anterior axillary line. It felt very hard, about the size of a hazel nut. The heart, lungs, and nervous system were normal. Gastric lavage gave a very dirty brown result.

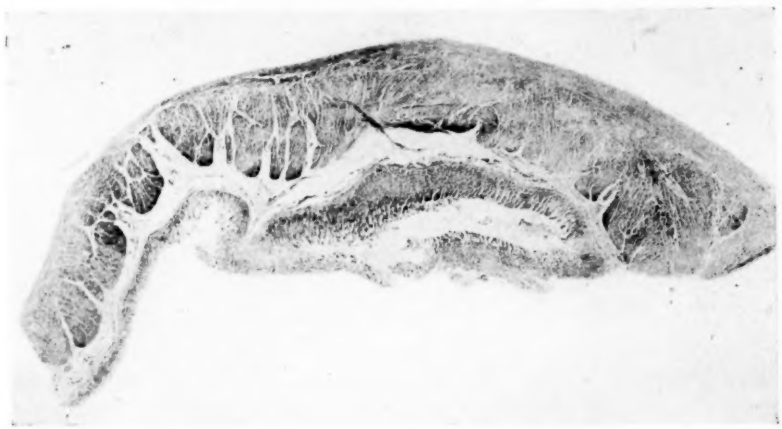
On account of the age of the child it was decided to adopt medical treatment. Thickened feeds were given two-hourly, with extra fluid a short time before feeds. Gastric lavage was performed daily.

COURSE. The temperature and pulse rate remained normal throughout. Vomiting continued in spite of treatment, though it diminished a little in severity, and on several days none occurred. No stool was passed during the first 36 hours in hospital. Subsequently the stools were normal in number, colour and consistency, suggesting that a proportion of the food taken was

passing the obstruction. The weight, after a temporary rise of a few ounces, became stationary and remained so until death. Gastric lavage almost always gave a large curdled thick result. On the 8th December the condition was not so good and a subcutaneous glucose saline was administered. On the 9th the child collapsed suddenly and passed a large light brown well-digested stool. A subcutaneous glucose saline was administered, but six hours later death occurred.

Post-mortem Examination. Performed 20 hours later. The stomach was very dilated and filled with gas. The pylorus was greatly hypertrophied for about 1½ inches (see Figures). It would not admit a probe, nor allow the passage of stomach contents. The rest of the gut was very small but normal in appearance except for slight injection of the mucosa.

Nothing abnormal was found in the rest of the body.

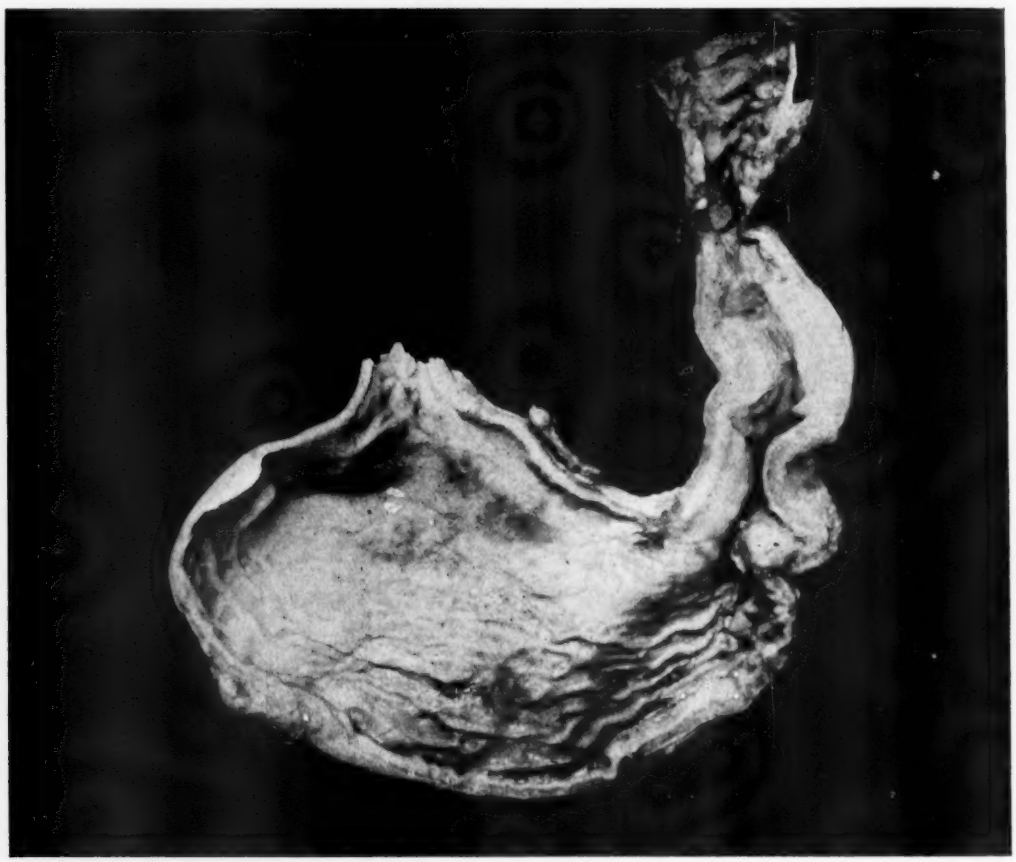


Section of the hypertrophied pylorus.

Discussion.

Congenital pyloric stenosis like many other diseases peculiar to childhood, displays a very clear-cut age-incidence. Most authorities regard it as a disease of infancy which, in the medically treated cases that survive, passes off spontaneously at the age of four or five months. 'Untreated cases die from starvation in the first few months of life, generally in the third month[1].' It is suggested, however, by Chapin and Royster[2] that when the stenosis is partial or slight, the attacks of vomiting may only occur at occasional intervals extending over a number of years. Unfortunately the authors do not give the evidence on which they base this statement. Oliver[3], Crohn[4], and others consider that the disease may in rare instances persist into adult life, but it would seem likely that such cases should be regarded as congenital malformations rather than true congenital hypertrophic stenosis of the pylorus, which is a very definite condition, remarkably self-limited. That the tumour may persist long after all symptoms of the disease have disappeared has been emphasized by Schlesinger[5], who palpated it in a child of 3½ years old. Only one case at all comparable to the above would appear to have been recorded in the literature. This case, reported by Davison[6], was normal until eight months old, when all the cardinal symptoms of pyloric stenosis developed, projectile vomiting, constipation, visible gastric peristalsis, and a palpable tumour. The extraordinarily

late onset of symptoms in this infant would suggest that the ætiology was not similar to that of ordinary congenital pyloric stenosis. Out of 463 cases of pyloric stenosis admitted to the Hospital for Sick Children, Great Ormond Street, during the ten years 1919-1929, only one other case presented symptoms of the disease at an age above five months. This patient was admitted under the



Photograph shewing the dilated stomach with the hypertrophied pylorus.

care of Dr. Still in 1921, at the age of six months and died three weeks later. The present case may therefore be considered as remarkable in that symptoms of obstruction were present as late as $7\frac{1}{2}$ months, the age at which death supervened. It is a question of some interest whether the seven weeks prematurity can have been a factor in determining the great prolongation. It is interesting to note that Dr. Still's case was a four weeks premature infant. It is probable that the date of onset of symptoms was in each case precipitated by the abnormally early functioning of the alimentary tract as a result of the premature birth. Measuring the age from the date of conception would then in part explain the peculiar senility of the two cases. This again might throw some light on the mechanism of the spontaneous recovery which occurs in those cases of pyloric stenosis which survive, adding support to the theory that the natural cure is effected by the growth of the pylorus. It is reasonable to expect

that this would be somewhat delayed in premature infants, few of which, however, would be likely to survive the severe degree of inanition which accompanies prolonged pyloric obstruction.

A fact of perhaps even greater interest was the intermittent character of the symptoms. Dr. Still[7] has emphasized this feature as additional evidence that the obstruction is at least in part due to spasm of the pylorus. He mentions cases in his experience in which infants suffering from pyloric stenosis had intervals of from two, three, or even as long as five days, when vomiting temporarily ceased entirely and food passed through the pylorus normally. Such instances must be clearly distinguished from those other not infrequent cases where vomiting ceases for twenty-four or forty-eight hours in some unexplained way as a result of a change in the diet; or where as the stomach dilates and the infant becomes weaker, vomiting diminishes in frequency and intensity, and may be quite absent for as many as twelve days in succession[8]. In such cases of course no improvement in the condition of the child occurs. No case would appear to have been recorded which will compare with the one reported here, in which the remissions were measured not in days, but in weeks and months.

Further proof of the part which spasm plays in causing the obstruction is furnished by the character of the stools in the present case during the two weeks preceding death. These demonstrated clearly that a considerable proportion of the food was beginning to pass the pylorus, the latter presumably relaxing as part of the terminal asthenia. It is likely therefore, that the appearance of more normal stools without improvement in the general condition of the child is to be regarded as of bad prognostic significance.

Lastly, this case raises the question of medical versus surgical treatment in older cases of congenital pyloric stenosis. Many advise against operating on infants of three or four months old, holding that such patients are approaching the point of spontaneous recovery. The case reported, though exceptional, shows that this reasoning may be fallacious, especially perhaps in the case of premature infants.

I am indebted to Dr. Robert Hutchison for permission to publish this case.

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CHLORIDES IN THE CEREBRO-SPINAL FLUID IN CASES OF MENINGITIS

BY

F. S. FOWWEATHER, M.D., M.Sc., F.I.C., D.P.H.

(From the Department of Pathology and Bacteriology, University of Leeds).

Since the discovery by Mestrezat that the chlorides of the cerebro-spinal fluid are reduced in meningitis, and to the greatest extent in tuberculous meningitis, a considerable amount of work has been devoted to this subject. As a result of the experience gained from this work the original claim of Mestrezat that values for chloride exceeding 0·64 per cent. absolutely exclude the diagnosis of tuberculous meningitis is no longer justified; the sharp distinction at first believed to be present between the results obtained in tuberculous meningitis and those found in the meningitis of other types does not exist.

I have examined the results obtained in this laboratory during the last three years, in cases of children, as well as the results published by other workers, and have arrived at the following conclusions :—

1. Reduction of chlorides is almost a constant finding in meningitis.
2. This reduction occurs, in general, to a greater degree in tuberculous meningitis than in other forms of meningitis.

So far as the analytical results themselves are concerned it may be said that :—

(a) Values below 0·59 per cent. are frequently found in tuberculous meningitis, but only very rarely in other forms. Linder and Carmichael[1] quote a case of chronic meningococcal meningitis in which the chloride was 0·52 per cent.

(b) Values between 0·59 per cent. and 0·64 per cent. are much more frequently found in tuberculous meningitis than in other forms.

(c) Values between 0·64 per cent. and 0·69 per cent., generally characteristic of acute purulent meningitis, may be found fairly frequently in tuberculous meningitis especially in the beginning of the illness, in which, however, there is often a rapid fall in chloride value with the progress of the disease.

Among the cases of meningitis which I have investigated, two appear to merit special attention, since they show that the reduction of the chloride may be the first change to be found in the cerebro-spinal fluid in such cases. This is a finding to which I have not previously seen any reference, but it appears to have some value from the point of view of diagnosis.

The most constant change in the cerebro-spinal fluid in meningitis has been considered to be an increase in the number of cells, and in the absence of such

an increase a diagnosis of meningitis would very rarely be made. No doubt such an increase can be demonstrated in a very great majority of cases and probably would occur in all cases at some stage of the disease if the patient lived long enough. But the two cases recorded here show that the appearance of this change is not absolutely constant ; it may in some cases be delayed, so that the reduction of chloride precedes it. The details of the cases are as follows :—

Case 1. Boy, aged 1 year, 8 months. An examination of the cerebro-spinal fluid on the day after admission showed 3 lymphocytes per c.mm. A further examination next day showed 4 lymphocytes per c.mm. On this occasion a chloride determination was carried out, the result being 0·62 per cent. Death occurred on the third day after admission.

A post-mortem examination by Prof. M. J. Stewart showed primary tracheo-bronchial gland tuberculosis ; advanced tuberculous basal meningitis with internal hydrocephalus ; acute miliary tuberculosis of lungs, liver and kidneys.

Case 2. Boy, aged 1 year. Two days after admission the cerebro-spinal fluid was found to contain 3 lymphocytes per c.mm. Eight days after admission 4 lymphocytes per c.mm. were found, while the chloride was found to be 0·65 per cent. Three days afterwards, in a fluid obtained shortly before death, about 2,500 cells per c.mm., mainly polymorphonuclear leucocytes, were found, while the chloride amounted to 0·62 per cent.

A post-mortem examination by Dr. R. H. Morley showed broncho-pneumonia ; right temporo-sphenoidal abscess ; generalized meningitis.

In the first case the reduction of chlorides was the only definite evidence of meningitis found in the cerebro-spinal fluid ; while in the second, reduction of chlorides, indicated the spread of inflammation from an abscess, causing generalized meningitis, before any indication of this condition was given by the cell count.

A third case in which no chloride estimations were made indicates the variability of the cell count in meningitis, and shows that normal counts may be obtained when meningitis is undoubtedly present.

Case 3. Girl, aged 3½ years. On the day after admission the cerebro-spinal fluid contained 15 lymphocytes per c.mm. Six days later, only 4 lymphocytes per c.mm. were found. Death occurred on the day after the latter examination.

A post-mortem examination by Prof. Stewart showed tuberculous meningitis ; fairly advanced caseous tuberculosis of the mesenteric glands ; a few miliary tubercles in the lungs.

In this case, while the first examination certainly showed an increase in the cell count, the result of the second examination was approximately normal, and if only the latter examination had been made no evidence of meningitis would have been obtained from the cerebro-spinal fluid. If a chloride determination had been made it is probable that a reduced value would have been found.

Nowicka[2] quotes a case in which a fluid was found to be normal so far as cells, albumin and sugar were concerned, but only 0·62 per cent. of chlorides, was present. The patient was a girl of 10 years, who had had Pott's disease some time previously. She was seriously ill when admitted, showing wasting, marked dyspnœa and generalized cyanosis. The temperature showed large, irregular variations, and there were abundant signs of disease in the lungs. She was considered to be suffering from acute tuberculosis. Death occurred after two weeks illness. No mention is made of any post-mortem examination.

Nowicka considers that the low chlorides in this case simply indicate a general reduction of chlorides throughout the body, but in view of the cases

mentioned above it seems probable that it may have been an early indication of the onset of tuberculous meningitis, for such a development as a terminal stage in tuberculous disease in children is, of course, of fairly frequent occurrence.

Linder and Carmichael[1] in a study of four cases of meningitis obtained results tending to show that the reduction of the chlorides in the cerebro-spinal fluid is accounted for by a parallel drop in the blood chlorides. It would therefore follow that low chlorides should be found in the cerebro-spinal fluid in any case in which the serum chlorides are reduced. But the frequency with which this occurs in conditions other than meningitis is not known, except in lobar pneumonia, in which low blood and cerebro-spinal fluid chlorides are the rule, and is probably not great ; whereas in meningitis the occurrence of low chlorides in the cerebro-spinal fluid is almost constant. As Greenfield[3] pointed out recently, the present views of the actual mechanism of the reduction of chloride in the cerebro-spinal fluid do not alter the significance of such a reduction from the prognostic standpoint : nor, I believe, do they make much difference to its significance with regard to diagnosis.

Conclusions.

The conclusions to be drawn from the cases I have described are :—

1. A normal cell-count in the cerebro-spinal fluid is not incompatible with the presence of meningitis.
2. A reduction of the chlorides in the cerebro-spinal fluid may be the first alteration to be found in cases of meningitis. In suspected cases, therefore, where the cell count is found to be normal, a chloride determination should be made before the diagnosis of meningitis is excluded.

I wish to express my thanks to Dr. C. W. Vining for his permission to use the records of cases under his care.

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